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(71) Applicant *(for all designated States except US)*: **CYTOVIA, INC.** [US/US]; 6650 NANCY RIDGE DRIVE, San Diego, CA 92121 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CAI, Sui, Xiong** [US/US]; 3623 BERRYFIELD COURT, San Diego, CA 92130 (US). **KEMNITZER, William, E.** [US/US]; 17161 ALVA ROAD, #311, San Diego, CA 92127 (US). **SIRISOMA, Nilantha, Sudath** [LK/US]; 6156 TAMILYNN STREET, San Diego, CA 92122 (US). **ZHANG, Han-zhong** [US/US]; 12683 RAGWEED STREET, San Diego, CA 92129 (US).

(74) Agents: **ESMOND, Robert, W.** et al.; STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C., 1100 NEW YORK AVENUE, N.W., Washington, DC 20005 (US).

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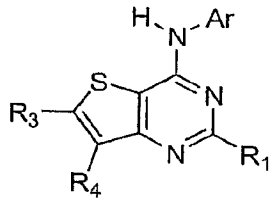
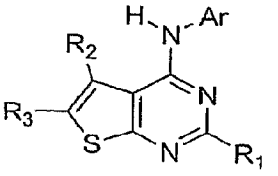


(I)



(II)

(57) Abstract: Disclosed are *N*-aryl-thienopyrimidin-4-amines and analogs thereof, represented by the Formulae I-II: wherein Ar and R_1-R_4 are defined herein. The present invention relates to the discovery that compounds having Formulae I-II are activators of caspases and inducers of apoptosis. Therefore, the activators of caspases and inducers of apoptosis of this invention may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs.

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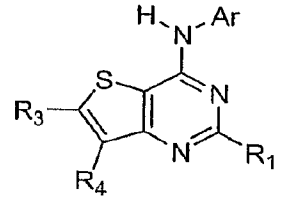
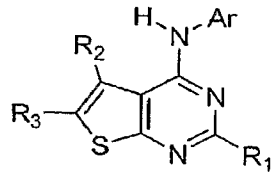
N-ARYL-THIENOPYRIMIDIN-4-AMINES AND ANALOGS AS ACTIVATORS OF CASPASES AND INDUCERS OF APOPTOSIS AND THE USE THEREOF

ABSTRACT OF THE DISCLOSURE

Disclosed are *N*-aryl-thienopyrimidin-4-amines and analogs thereof, represented by the Formulae I-II:



(I)



(II)

wherein Ar and R_1-R_4 are defined herein. The present invention relates to the discovery that compounds having Formulae I-II are activators of caspases and inducers of apoptosis. Therefore, the activators of caspases and inducers of apoptosis of this invention may be used to induce cell death in a variety of clinical conditions in which uncontrolled growth and spread of abnormal cells occurs.

N-ARYL-THIENOPYRIMIDIN-4-AMINES AND ANALOGS AS ACTIVATORS OF CASPASES AND INDUCERS OF APOPTOSIS AND THE USE THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention is in the field of medicinal chemistry. In particular, the invention relates to *N*-aryl-thienopyrimidin-4-amines and analogs, and the discovery that these compounds are activators of caspases and inducers of apoptosis. The invention also relates to the use of these compounds as therapeutically effective anti-cancer agents.

Related Art

[0002] Organisms eliminate unwanted cells by a process variously known as regulated cell death, programmed cell death or apoptosis. Such cell death occurs as a normal aspect of animal development, as well as in tissue homeostasis and aging (Glucksmann, A., *Biol. Rev. Cambridge Philos. Soc. 26*:59-86 (1951); Glucksmann, A., *Archives de Biologie 76*:419-437 (1965); Ellis, *et al., Dev. 112*:591-603 (1991); Vaux, *et al., Cell 76*:777-779 (1994)). Apoptosis regulates cell number, facilitates morphogenesis, removes harmful or otherwise abnormal cells and eliminates cells that have already performed their function. Additionally, apoptosis occurs in response to various physiological stresses, such as hypoxia or ischemia (PCT published application WO96/20721).

[0003] There are a number of morphological changes shared by cells experiencing regulated cell death, including plasma and nuclear membrane blebbing, cell shrinkage (condensation of nucleoplasm and cytoplasm), organelle relocalization and compaction, chromatin condensation and production of apoptotic bodies (membrane enclosed particles containing intracellular material) (Orrenius, S., *J. Internal Medicine 237*:529-536 (1995)).

[0004] Apoptosis is achieved through an endogenous mechanism of cellular suicide (Wyllie, A.H., in *Cell Death in Biology and Pathology*, Bowen and Lockshin, eds., Chapman and Hall (1981), pp. 9-34). A cell activates its internally encoded suicide

program as a result of either internal or external signals. The suicide program is executed through the activation of a carefully regulated genetic program (Wyllie, *et al.*, *Int. Rev. Cyt. 68:*251 (1980); Ellis, *et al.*, *Ann. Rev. Cell Bio. 7:*663 (1991)). Apoptotic cells and bodies are usually recognized and cleared by neighboring cells or macrophages before lysis. Because of this clearance mechanism, inflammation is not induced despite the clearance of great numbers of cells (Orrenius, S., *J. Internal Medicine 237*:529-536 (1995)).

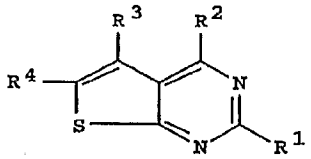
[0005] It has been found that a group of proteases are a key element in apoptosis (see, e.g., Thornberry, *Chemistry and Biology 5*:R97-R103 (1998); Thornberry, *British Med. Bull. 53*:478-490 (1996)). Genetic studies in the nematode *Caenorhabditis elegans* revealed that apoptotic cell death involves at least 14 genes, 2 of which are the pro-apoptotic (death-promoting) *ced* (for *cell death abnormal*) genes, *ced-3* and *ced-4*. CED-3 is homologous to interleukin 1 beta-converting enzyme, a cysteine protease, which is now called caspase-1. When these data were ultimately applied to mammals, and upon further extensive investigation, it was found that the mammalian apoptosis system appears to involve a cascade of caspases, or a system that behaves like a cascade of caspases. At present, the caspase family of cysteine proteases comprises 14 different members, and more may be discovered in the future. All known caspases are synthesized as zymogens that require cleavage at an aspartyl residue prior to forming the active enzyme. Thus, caspases are capable of activating other caspases, in the manner of an amplifying cascade.

[0006] Apoptosis and caspases are thought to be crucial in the development of cancer (*Apoptosis and Cancer Chemotherapy*, Hickman and Dive, eds., Humana Press (1999)). There is mounting evidence that cancer cells, while containing caspases, lack parts of the molecular machinery that activates the caspase cascade. This makes the cancer cells lose their capacity to undergo cellular suicide and the cells become cancerous. In the case of the apoptosis process, control points are known to exist that represent points for intervention leading to activation. These control points include the CED-9-BCL-like and CED-3-ICE-like gene family products, which are intrinsic proteins regulating the decision of a cell to survive or die and executing part of the cell death process itself, respectively (see, Schmitt, *et al.*, *Biochem. Cell. Biol. 75*:301-314 (1997)). BCL-like proteins include BCL-xL and BAX-alpha, which appear to function upstream of caspase activation. BCL-xL appears to prevent activation of the

apoptotic protease cascade, whereas BAX-alpha accelerates activation of the apoptotic protease cascade.

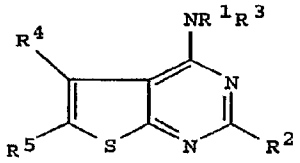
[0007] It has been shown that chemotherapeutic (anti-cancer) drugs can trigger cancer cells to undergo suicide by activating the dormant caspase cascade. This may be a crucial aspect of the mode of action of most, if not all, known anticancer drugs (Los, *et al., Blood 90*:3118-3129 (1997); Friesen, *et al., Nat. Med. 2*:574 (1996)). The mechanism of action of current antineoplastic drugs frequently involves an attack at specific phases of the cell cycle. In brief, the cell cycle refers to the stages through which cells normally progress during their lifetime. Normally, cells exist in a resting phase termed G_o. During multiplication, cells progress to a stage in which DNA synthesis occurs, termed S. Later, cell division, or mitosis occurs, in a phase called M. Antineoplastic drugs, such as cytosine arabinoside, hydroxyurea, 6-mercaptopurine, and methotrexate are S phase specific, whereas antineoplastic drugs, such as vincristine, vinblastine, and paclitaxel are M phase specific. Many slow growing tumors, e.g. colon cancers, exist primarily in the G_o phase, whereas rapidly proliferating normal tissues, for example bone marrow, exist primarily in the S or M phase. Thus, a drug like 6-mercaptopurine can cause bone marrow toxicity while remaining ineffective for a slow growing tumor. Further aspects of the chemotherapy of neoplastic diseases are known to those skilled in the art (*see*, e.g., Hardman, *et al.*, eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Ninth Edition, McGraw-Hill, New York (1996), pp. 1225-1287). Thus, it is clear that the possibility exists for the activation of the caspase cascade, although the exact mechanisms for doing so are not clear at this point. It is equally clear that insufficient activity of the caspase cascade and consequent apoptotic events are implicated in various types of cancer. The development of caspase cascade activators and inducers of apoptosis is a highly desirable goal in the development of therapeutically effective antineoplastic agents. Moreover, since autoimmune disease and certain degenerative diseases also involve the proliferation of abnormal cells, therapeutic treatment for these diseases could also involve the enhancement of the apoptotic process through the administration of appropriate caspase cascade activators and inducers of apoptosis.

[0008] EP447891 discloses the preparation of thieno[2,3-*d*]pyrimidines as pesticides, herbicides, and plant growth regulators:



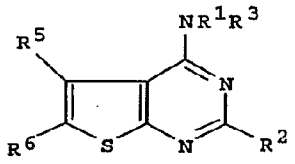
wherein, R_1 = H, C_{1-5} alkyl, C_{1-3} chloroalkyl, C_{3-6} cycloalkyl, Ph, CH_2Ph; R_2 = F, Cl, Br, iodo, OH, N_3, NR_5R_6, etc.; R_3 = Cl, Br, OH, SH; R_4 = H, C_{1-6} alkyl, C_{3-6} haloalkyl, Ph, cyano, CHO, CO_2H, etc.; R_5,R_6 = H, NH_2, org. group or NR_5R_6 = 3-8 membered heterocyclyl.

[0009] US4196207 discloses 4-aminothieno[2,3-*d*]pyrimidine derivatives for the control or eradication of ixodid ticks:



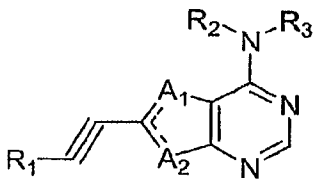
wherein, R_1 = alkyl, alkylaryl, hydroxyalkyl, etc.; R_2 = H, OH, SH, halo, CN, etc.; R_3 = H, alkyl, or acyl; R_4 and R_5 = H, alkyl, halo, etc.; R_4R_5 = alkylene.

[0010] US4146716 discloses thienopyrimidine derivative compositions for controlling fungal, viral and bacterial plant diseases and insect damage:



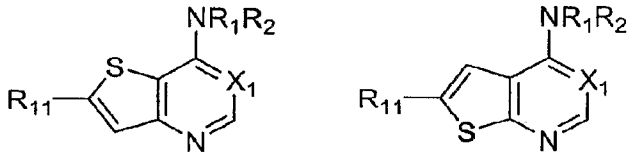
wherein, R_1 = H, alkyl, alkylaryl, etc.; R_2 = H, Cl, $NHNH_2$, heterocyclic radical, NH_2, Me, Et, Ph, etc.; R_3 = H, Me, Et, NH_2, etc.; R_5 = H or Me; R_6 = H, Me, Ph, NHAc, etc.; $R_5R_6 = (CH_2)_4$.

[0011] WO05007083 discloses the preparation of thienopyrimidine derivatives as ErbB kinase inhibitors:



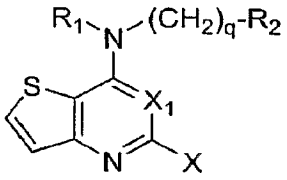
wherein, one of A_1 and A_2 is S and the other is CH; R_1 for example is a substituted heterocyclyl or heterocyclylene; R_2 is H, alkyl, CO-alkyl; R_3 is -Q-$(Q_1)_r$-$(Q_2)_t$; Q is hetero/arylene, aryl, aralkyl; Q_1 = O, SO_2, S; r = 0-1; Q_2 = aralkyl, hetero/aryl; t = 0-1.

[0012] US6492383 and WO9924440 discloses derivatives of thienopyrimidine and thienopyrimidine derivatives useful as anticancer agents:



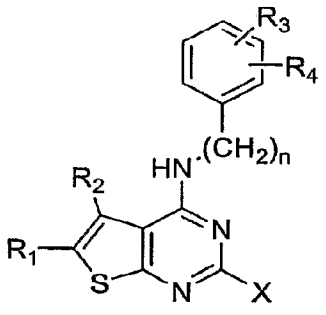
wherein, for example, X_1 is N or CH, R_1 is H or C_1-C_6 alkyl, R_2 is C_6-C_{10} aryl, R_{11} is H, C_1-C_6 alkyl, -$(CH_2)_t$(C_6-C_{10} aryl). Preferred R_{11} is -$(CH_2)_t$(C_6-C_{10} aryl).

[0013] WO03055890 discloses thienopyrimidine derivatives as inhibitors of prolylpeptidase, inducers of apoptosis and cancer treatment agents:



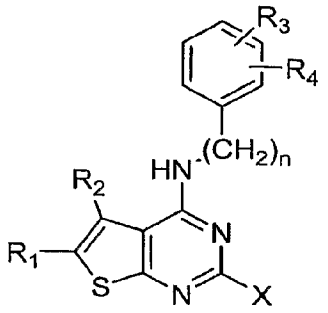
wherein, X is OR_3 or NR_3R_4, R_1 is H or C_1-C_5 alkyl, R_2 for example is phenyl, q is 0-1.

[0014] US6130223 discloses thienopyrimidine with phophodiesterse V inhibiting effect:



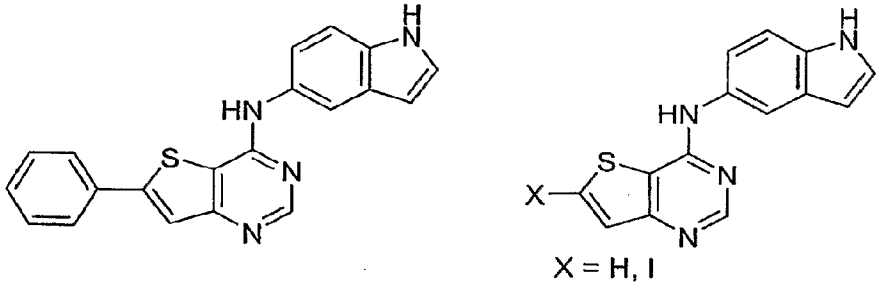
wherein, for example R_1, R_2 are H or alkenyl, R_3, R_4 are H or NH_2, X is a 5- to 7-menbered saturated heterocyclic ring, n is 0, 1, 2, or 3.

[0015] US6133271 discloses method for inhibiting neoplastic cells and related conditions by exposure to thienopyrimidine derivatives:

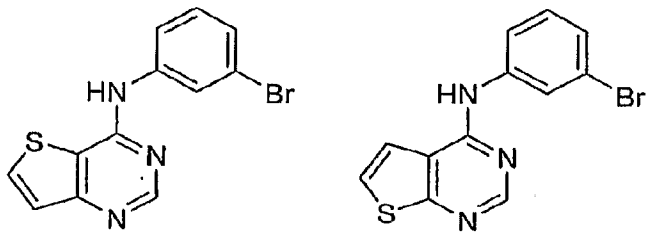


wherein, for example R_1, R_2 are H or alkenyl, R_3, R_4 are H or NH_2, X is a 5-7 membered saturated or unsaturated heterocyclic ring, n is 0, 1, 2, or 3.

[0016] Munchhof *et al.* (*Bioorg. Med. Chem. Lett. 14*:21-24 (2004)) reported thienopyrimidine and thienopyridine as inhibitors of VEGFR-2 kinase. It was reported that the phenyl group in the 6-position increases the inhibiting activity at VEGFR-2 kinase by about 20-fold vs the corresponding 6-H analog. The 5-indolylamino group in the 4-position also is critical for the inhibiting activity.



[0017] Showalter *et al.* (*J. Med. Chem. 42*:5464-5474 (1999)) reported several heterocycles as inhibitors of the epidermal growth factor receptor tyrosine kinase. It was reported that *N*-(3-bromophenyl)-thieno[3,2-*d*]pyrimidine and *N*-(3-bromophenyl)-thieno[2,3-*d*]pyrimidine are potent inhibitors of the epidermal growth factor receptor tyrosine kinase (IC_{50} values of 11 and 35 nM, respectively).



SUMMARY OF THE INVENTION

[0018] The present invention is related to the discovery that *N*-aryl-thienopyrimidin-4-amines and analogs, as represented in Formulae I-IV, are activators of the caspase cascade and inducers of apoptosis. Thus, an aspect of the present invention is directed to the use of compounds of Formulae I-IV as inducers of apoptosis.

[0019] A second aspect of the present invention is to provide a method for treating, preventing or ameliorating neoplasia and cancer by administering a compound of one of the Formulae I-IV to a mammal in need of such treatment.

[0020] Many of the compounds within the scope of the present invention are novel compounds. Therefore, a third aspect of the present invention is to provide novel compounds of Formulae I-IV, and to also provide for the use of these novel compounds for treating, preventing or ameliorating neoplasia and cancer.

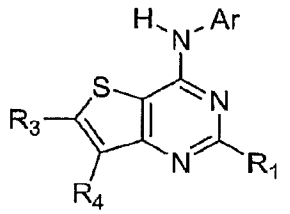
[0021] A fourth aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the induction of apoptosis, containing an effective amount of a compound of one of the Formulae I-IV in admixture with one or more pharmaceutically acceptable carriers or diluents.

[0022] A fifth aspect of the present invention is directed to methods for the preparation of novel compounds of Formulae I-IV.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention arises out of the discovery that *N*-aryl-thienopyrimidin-4-amines and analogs, as represented in Formulae I-IV, are potent and highly efficacious activators of the caspase cascade and inducers of apoptosis. Therefore, compounds of Formulae I-IV are useful for treating disorders responsive to induction of apoptosis.

[0024] Specifically, compounds of the present invention are represented by Formula I:



(I)

or pharmaceutically acceptable salts or prodrugs or tautomers thereof, wherein:

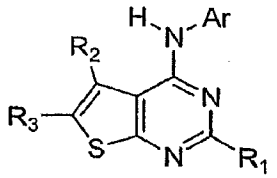
[0025] Ar is optionally substituted aryl or optionally substituted heteroaryl;

[0026] R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol; and

[0027] R_3-R_4 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

[0028] Preferred compounds of Formula I include compounds wherein Ar is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, isoxazolyl, pyrazolyl, imidazolyl, thienyl, furyl or pyrrolyl, each of which is optionally substituted. More preferably, Ar is phenyl or pyridyl. Another group of preferred compounds of Formula I include compounds wherein R_3 is hydrogen or halo. Another group of preferred compounds of Formula I include compounds wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

[0029] Another group of compounds of the present invention are represented by Formula II:



(II)

or pharmaceutically acceptable salts, prodrugs or tautomers thereof, wherein:

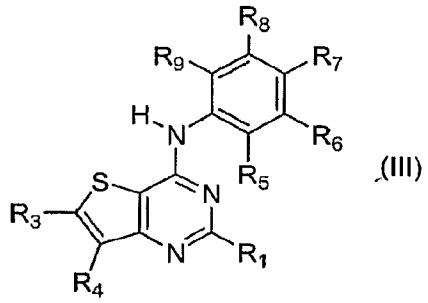
[0030] Ar is optionally substituted aryl or optionally substituted heteroaryl;

[0031] R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol; and

[0032] R_2-R_3 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

[0033] Preferred compounds of Formula II include compounds wherein R_2 is hydrogen. Another group of preferred compounds of Formula II include compounds wherein Ar is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, isoxazolyl, pyrazolyl, imidazolyl, thienyl, furyl or pyrrolyl, each of which is optionally substituted. More preferably, Ar is phenyl or pyridyl. Another group of preferred compounds of Formula II include compounds wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

[0034] One group of preferred compounds of the present invention are represented by Formula III:



(III)

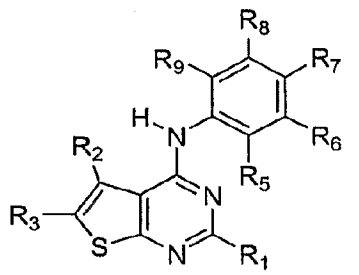
or pharmaceutically acceptable salts, prodrugs or tautomers thereof, wherein:

[0035] R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol; and

[0036] R_3-R_9 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

[0037] Preferred compounds of Formula III include compounds wherein one of the R_6 and R_8 is alkoxy or amino, or both R_6 and R_8 are alkoxy. Another group of preferred compounds of Formula III include compounds wherein R_3 is hydrogen or halo. Another group of preferred compounds of Formula III include compounds wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

[0038] Another group of preferred compounds of the present invention are represented by Formula IV:



(IV)

or pharmaceutically acceptable salts, prodrugs or tautomers thereof, wherein:

[0039] R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol; and

[0040] R_2-R_3 and R_5-R_9 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

[0041] Preferred compounds of Formula IV include compounds wherein R_2 is hydrogen. Another group of preferred compounds of Formula IV include compounds wherein one of the R_6 and R_8 is alkoxy or amino, or both R_6 and R_8 are alkoxy. Another group of preferred compounds of Formula IV include compounds wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

[0042] Exemplary preferred compounds of Formulae I-IV that may be employed in the method of the invention include, without limitation:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2-methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate;

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride;

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-thieno[2,3-*d*]pyrimidin-4-amine;

and pharmaceutically acceptable salts or prodrugs thereof.

[0043] The present invention is also directed to novel compounds within the scope of Formulae I-IV. Exemplary preferred compounds that may be employed in this invention include, without limitation:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,3-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(4-Methoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(4-Methoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(4-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Methylisoxazol-3-yl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(4-Methoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine;

3-[4-(Thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl]acrylic acid ethyl ester;

N-(2,5-Dimethoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(5-Methoxy-2-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-Methoxy-5-phenoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

4-Methoxy-3-(thieno[3,2-*d*]pyrimidin-4-ylamino)-benzoic acid;

N-(2-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dihydroxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate;

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Bis(methylsulfonyl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,6-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride;

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Amino-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-thieno[2,3-*d*]pyrimidin-4-amine;

and pharmaceutically acceptable salts or prodrugs thereof.

[0044] The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to ten carbons. Useful alkyl groups include straight-chained and branched C_{1-10} alkyl groups, more preferably C_{1-6} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, 3-pentyl, hexyl and octyl groups, which may be optionally substituted.

[0045] The term "alkenyl" as employed herein by itself or as part of another group means a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including at least one double bond between two of the carbon atoms in the chain. Typical alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

[0046] The term "alkynyl" is used herein to mean a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain. Typical alkynyl

groups include ethynyl, 1-propynyl, 1-methyl-2-propynyl, 2-propynyl, 1-butynyl and 2-butynyl.

[0047] Useful alkoxy groups include oxygen substituted by one of the C_{1-10} alkyl groups mentioned above, which may be optionally substituted. Alkoxy substituents include, without limitation, halo, morpholino, amino including alkylamino and dialkylamino, and carboxy including esters thereof.

[0048] Useful alkylthio groups include sulfur substituted by one of the C_{1-10} alkyl groups mentioned above, which may be optionally substituted. Also included are the sulfoxides and sulfones of such alkylthio groups.

[0049] Useful amino and optionally substituted amino groups include $-NH_2$, $-NHR_{15}$ and $-NR_{15}R_{16}$, wherein R_{15} and R_{16} are C_{1-10} alkyl or cycloalkyl groups, or R_{15} and R_{16} are combined with the N to form a ring structure, such as a piperidine, or R_{15} and R_{16} are combined with the N and other group to form a ring, such as a piperazine. The alkyl group may be optionally substituted.

[0050] Optional substituents on the alkyl, alkoxy, alkylthiol, alkenyl, alkynyl, cycloalkyl, carbocyclic and heterocyclic groups include one or more halo, hydroxy, carboxyl, amino, nitro, cyano, C_1-C_6 acylamino, C_1-C_6 acyloxy, C_1-C_6 alkoxy, aryloxy, alkylthio, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, saturated and unsaturated heterocyclic or heteroaryl.

[0051] Optional substituents on the aryl, arylalkyl, arylalkenyl, arylalkynyl and heteroaryl and heteroarylalkyl groups include one or more halo, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_4-C_7 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl(C_1-C_6)alkyl, C_6-C_{10} aryl(C_2-C_6)alkenyl, C_6-C_{10} aryl(C_2-C_6)alkynyl, C_1-C_6 hydroxyalkyl, nitro, amino, ureido, cyano, C_1-C_6 acylamino, hydroxy, thiol, sulfone, sulfoxide, C_1-C_6 acyloxy, (C_1-C_6)alkoxycarbonyl (C_2-C_6)alkenyl, azido, C_1-C_6 alkoxy or carboxy.

[0052] The term "aryl" as employed herein by itself or as part of another group refers to monocyclic, bicyclic or tricyclic aromatic groups containing from 6 to 14 carbons in the ring portion.

[0053] Useful aryl groups include C_{6-14} aryl, preferably C_{6-10} aryl. Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthrenyl, anthracenyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

[0054] The term "carbocycle" as employed herein include cycloalkyl and partially saturated carbocyclic groups. Useful cycloalkyl groups are C_{3-8} cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0055] Useful saturated or partially saturated carbocyclic groups are cycloalkyl groups as described above, as well as cycloalkenyl groups, such as cyclopentenyl, cycloheptenyl and cyclooctenyl.

[0056] Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

[0057] The term "arylalkyl" is used herein to mean any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Preferably the arylalkyl group is benzyl, phenethyl or naphthylmethyl.

[0058] The term "arylalkenyl" is used herein to mean any of the above-mentioned C_{2-10} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

[0059] The term "arylalkynyl" is used herein to mean any of the above-mentioned C_{2-10} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

[0060] The term "aryloxy" is used herein to mean oxygen substituted by one of the above-mentioned C_{6-14} aryl groups, which may be optionally substituted. Useful aryloxy groups include phenoxy and 4-methylphenoxy.

[0061] The term "arylalkoxy" is used herein to mean any of the above mentioned C_{1-10} alkoxy groups substituted by any of the above-mentioned aryl groups, which may be optionally substituted. Useful arylalkoxy groups include benzyloxy and phenethyloxy.

[0062] Useful haloalkyl groups include C_{1-10} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, chloromethyl, chlorofluoromethyl and trichloromethyl groups.

[0063] Useful acylamino (acylamido) groups are any C_{1-6} acyl (alkanoyl) attached to an amino nitrogen, e.g., acetamido, chloroacetamido, propionamido, butanoylamido, pentanoylamido and hexanoylamido, as well as aryl-substituted C_{1-6} acylamino groups, e.g., benzoylamido, and pentafluorobenzoylamido.

[0064] Useful acyloxy groups are any C_{1-6} acyl (alkanoyl) attached to an oxy (–O–) group, e.g., formyloxy, acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy and hexanoyloxy.

[0065] The term heterocycle is used herein to mean a saturated or partially saturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or on a nitrogen atom if the resulting compound is stable.

[0066] Useful saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl pyrazolinyl, tetronoyl and tetramoyl groups.

[0067] The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms.

[0068] Useful heteroaryl groups include thienyl (thiophenyl), benzo[*b*]thienyl, naphtho[2,3-*b*]thienyl, thianthrenyl, furyl (furanyl), pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, including without limitation 2*H*-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), including without limitation 2-pyridyl, 3-pyridyl, and 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-*a*]pyrimidin-4-one, pyrazolo[1,5-*a*]pyrimidinyl, including without limitation pyrazolo[1,5-*a*]pyrimidin-3-yl, 1,2-benzoisoxazol-3-yl,- benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an *N*-oxide, e.g., a pyridyl *N*-oxide, pyrazinyl *N*-oxide and pyrimidinyl *N*-oxide.

[0069] The term "heteroaryloxy" is used herein to mean oxygen substituted by one of the above-mentioned heteroaryl groups, which may be optionally substituted. Useful

heteroaryloxy groups include pyridyloxy, pyrazinyloxy, pyrrolyloxy, pyrazolyloxy, imidazolyloxy and thiophenyloxy.

[0070] The term "heteroarylalkoxy" is used herein to mean any of the above-mentioned C_{1-10} alkoxy groups substituted by any of the above-mentioned heteroaryl groups, which may be optionally substituted.

[0071] Some of the compounds of the present invention may exist as stereoisomers including optical isomers. The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

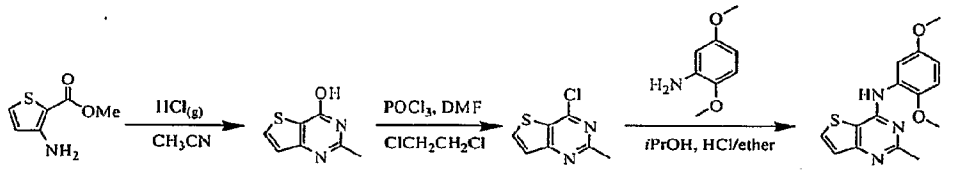
[0072] Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts, such as hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate and oxalate; and inorganic and organic base addition salts with bases, such as sodium hydroxy, Tris(hydroxymethyl)aminomethane (TRIS, tromethane) and *N*-methyl-glucamine.

[0073] Examples of prodrugs of the compounds of the invention include the simple esters of carboxylic acid containing compounds (e.g., those obtained by condensation with a C_{1-4} alcohol according to methods known in the art); esters of hydroxy containing compounds (e.g., those obtained by condensation with a C_{1-4} carboxylic acid, C_{3-6} dioic acid or anhydride thereof, such as succinic and fumaric anhydrides according to methods known in the art); imines of amino containing compounds (e.g., those obtained by condensation with a C_{1-4} aldehyde or ketone according to methods known in the art); carbamate of amino containing compounds, such as those described by Leu, *et. al.*, (*J. Med. Chem. 42*:3623-3628 (1999)) and Greenwald, *et. al.*, (*J. Med. Chem. 42*:3657-3667 (1999)); and acetals and ketals of alcohol containing compounds (e.g., those obtained by condensation with chloromethyl methyl ether or chloromethyl ethyl ether according to methods known in the art).

[0074] The compounds of this invention may be prepared using methods known to those skilled in the art, or the novel methods of this invention. Specifically, the compounds of this invention with Formulae I-IV can be prepared as illustrated by the exemplary reaction in Scheme 1. 4-Chloro-2-methylthieno[3,2-*d*]pyrimidine was prepared by reaction of 3-amino-thiophene-2-carboxylic acid methyl ester and anhydrous acetonitrile in the presence of HCl to produce 2-methylthieno[3,2-

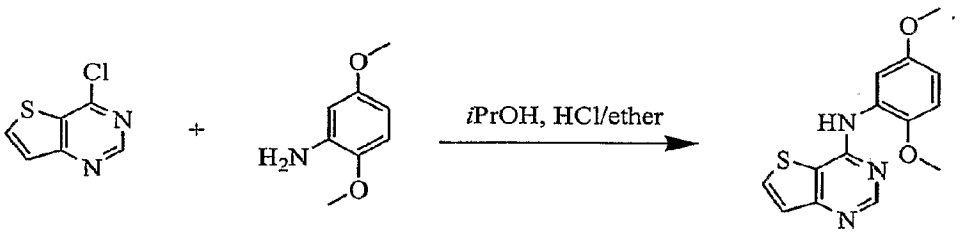
d]pyrimidin-4-ol, followed by treatment of 2-methylthieno[3,2-*d*]pyrimidin-4-ol with distilled phosphorous oxychloride in the presence of anhydrous dimethylformamide and 1,2-dichloroethane. Reaction of 4-chloro-2-methylthieno[3,2-*d*]pyrimidine with a substituted aniline such as 2,5-dimethoxyaniline, in *i*-propanol (*i*-PrOH) in the presence of HCl produced *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine.

Scheme 1



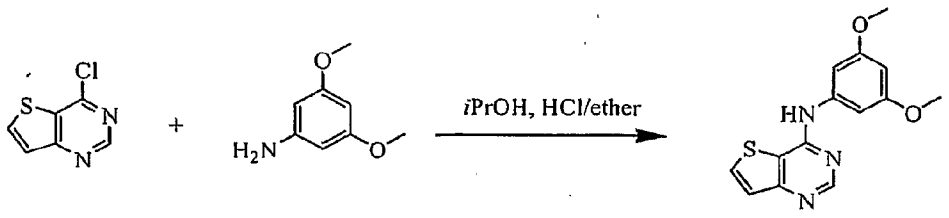
[0075] Other compounds of this invention could be prepared similarly as illustrated by the exemplary reaction in Scheme 2. Reaction of 4-chloro-thieno[3,2-*d*]pyrimidine with a substituted aniline such as 2,5-dimethoxyaniline, produced *N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine.

Scheme 2



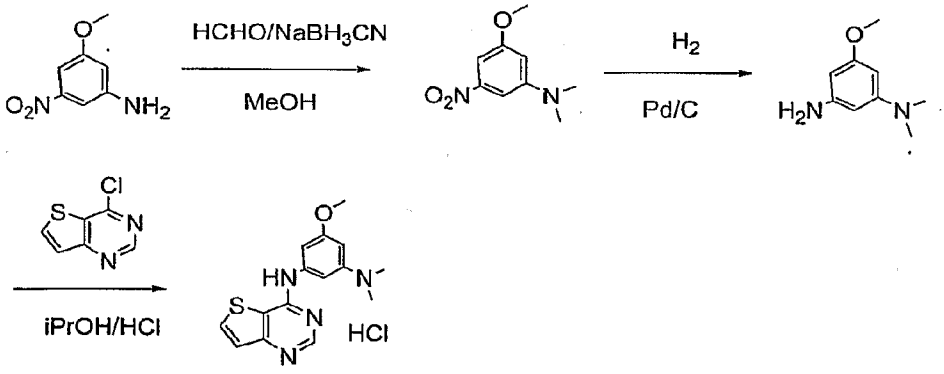
[0076] Similarly, other compounds of this invention could be prepared as illustrated by the exemplary reaction in Scheme 3. Reaction of 4-chloro-thieno[3,2-*d*]pyrimidine with a substituted aniline such as 3,5-dimethoxyaniline, produced *N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine.

Scheme 3



[0077] Compounds of this invention also could be prepared as illustrated by the exemplary reaction in Scheme 4. Reaction of 3-methoxy-5-nitroaniline in a solvent such as methanol in the presence of an acid such as acetic acid with aqueous formaldehyde and sodium cyanoborohydride produced *N,N*-dimethyl-3-methoxy-5-nitroaniline. Reduction of the nitro group by hydrogenation in the presence of 5% palladium on carbon and concentrated hydrochloride produced the aniline as a hydrochloride salt. Reaction of the aniline with 4-chlorothieno[3,2-*d*]pyrimidine in isopropanol in the presence of HCl produced *N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine as its hydrochloride salt.

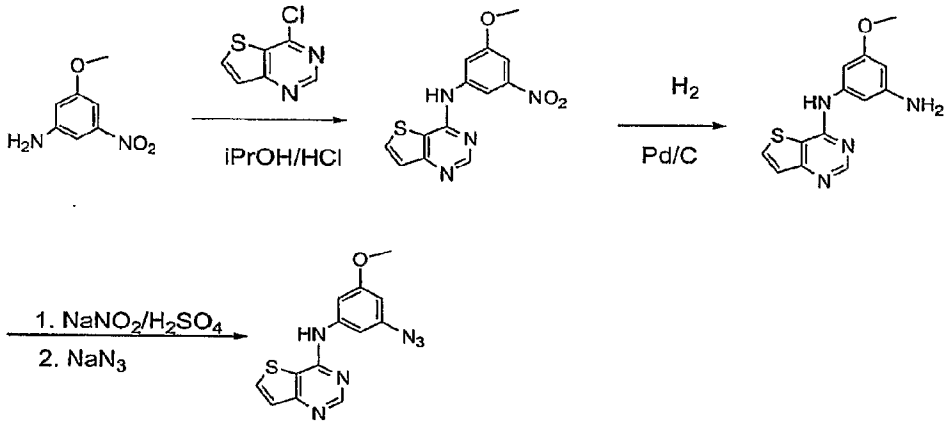
Scheme 4



[0078] Compounds of this invention also could be prepared as illustrated by the exemplary reaction in Scheme 5. Reaction of 4-chloro-thieno[3,2-*d*]pyrimidine with a substituted aniline such as 3-methoxy-5-nitroaniline produced *N*-(3-methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine. Reduction of the nitro group by hydrogenation in the presence of 5% palladium on carbon and concentrated hydrochloride produced the aniline as a hydrochloride salt. Reaction of the aniline

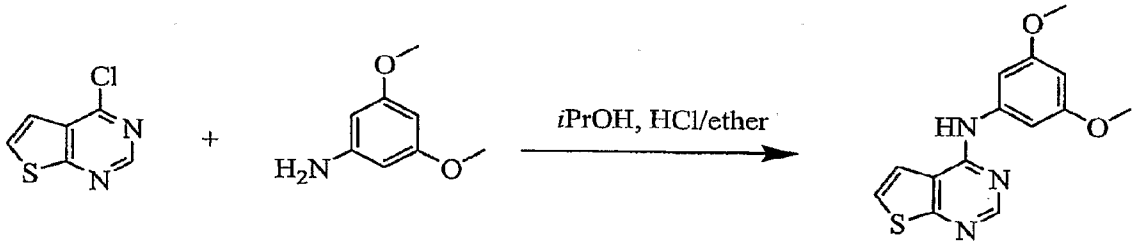
with sodium nitrite in concentrated sulfuric acid, followed by treatment with sodium azide, produced the azido compound.

Scheme 5



[0079] Similarly, other compounds of this invention could be prepared as illustrated by the exemplary reaction in Scheme 6. Reaction of 4-chloro-thieno[2,3-*d*]pyrimidine with a substituted aniline such as 3,5-dimethoxyaniline, produced *N*-(3,5-dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine.

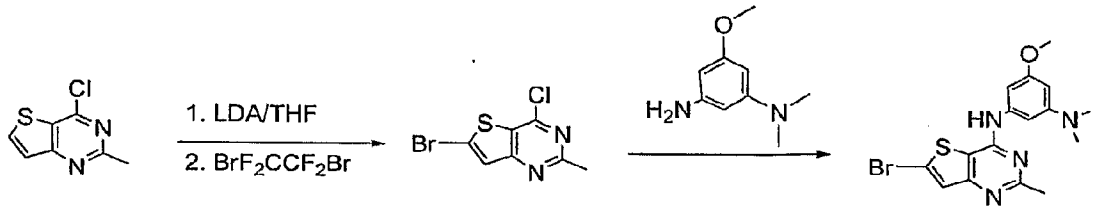
Scheme 6



[0080] Similarly, other compounds of this invention could be prepared as illustrated by the exemplary reaction in Scheme 7. Reaction of 4-chloro-2-methylthieno[3,2-*d*]pyrimidine with lithium diisopropylamide followed by treatment with 1,2-dibromo-1,1,2,2-tetrafluoroethane produced 6-bromo-4-chloro-2-methylthieno[3,2-*d*]pyrimidine. Reaction of 6-bromo-4-chloro-2-methylthieno[3,2-*d*]pyrimidine with a substituted aniline such as 5-methoxy-*N1*,*N1*-dimethylbenzene-1,3-diamine, produced

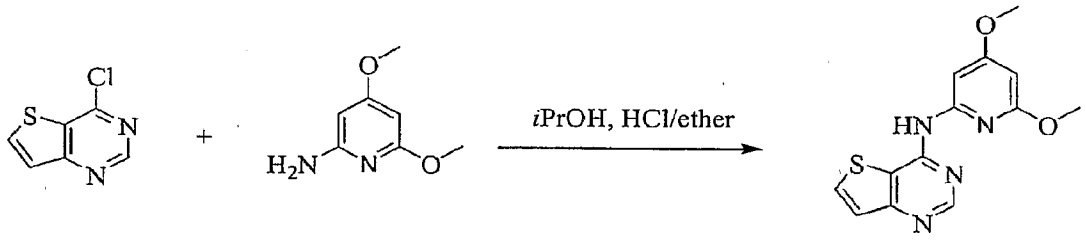
6-bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine.

Scheme 7



[0081] Similarly, compounds of this invention could be prepared as illustrated by the exemplary reaction in Scheme 8. Reaction of 4-chloro-thieno[3,2-*d*]pyrimidine with a substituted pyridine-amine such as 4,6-dimethoxypyridin-2-amine, should produce *N*-(4,6-dimethoxypyridin-2-yl)thieno[3,2-*d*]pyrimidin-4-amine.

Scheme 8



[0082] An important aspect of the present invention is the discovery that compounds having Formulae I-IV are activators of caspases and inducers of apoptosis. Therefore, these compounds are useful in a variety of clinical conditions in which there is uncontrolled cell growth and spread of abnormal cells, such as in the case of cancer.

[0083] Another important aspect of the present invention is the discovery that compounds having Formulae I-IV are potent and highly efficacious activators of caspases and inducers of apoptosis in drug resistant cancer cells, such as breast and prostate cancer cells, which enables these compounds to kill these drug resistant cancer cells. In comparison, most standard anti-cancer drugs are not effective in killing drug resistant cancer cells under the same conditions. Therefore, compounds of

this invention are useful for the treatment of drug resistant cancer, such as breast cancer in animals.

[0084] The present invention includes a therapeutic method useful to modulate *in vivo* apoptosis or *in vivo* neoplastic disease, comprising administering to a subject in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis.

[0085] The present invention also includes a therapeutic method comprising administering to an animal an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of said compound of Formulae I-IV, wherein said therapeutic method is useful to treat cancer, which is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Such diseases include, but are not limited to, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoides, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, and prostatic carcinoma.

[0086] In practicing the therapeutic methods, effective amounts of compositions containing therapeutically effective concentrations of the compounds formulated for oral, intravenous, local and topical application, for the treatment of neoplastic diseases and other diseases in which caspase cascade mediated physiological responses are implicated, are administered to an individual exhibiting the symptoms of one or more of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders. An effective amount of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner

reduce, the symptoms associated with the disease. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective. The amount may cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve the desired amelioration of symptoms.

[0087] In another embodiment, a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt of said compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis in combination with a pharmaceutically acceptable vehicle is provided.

[0088] Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of said compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known cancer chemotherapeutic agent, or a pharmaceutically acceptable salt of said agent. Examples of known cancer chemotherapeutic agents which may be used for combination therapy include, but not are limited to alkylating agents, such as busulfan, cis-platin, mitomycin C, and carboplatin; antimitotic agents, such as colchicine, vinblastine, paclitaxel, and docetaxel; topo I inhibitors, such as camptothecin and topotecan; topo II inhibitors, such as doxorubicin and etoposide; RNA/DNA antimetabolites, such as 5-azacytidine, 5-fluorouracil and methotrexate; DNA antimetabolites, such as 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea and thioguanine; antibodies, such as campath, Herceptin® or Rituxan®. Other known cancer chemotherapeutic agents which may be used for combination therapy include melphalan, chlorambucil, cyclophosamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, Gleevec® and alanosine.

[0089] In practicing the methods of the present invention, the compound of the invention may be administered together with at least one known chemotherapeutic agent as part of a unitary pharmaceutical composition. Alternatively, the compound of the invention may be administered apart from at least one known cancer chemotherapeutic agent. In one embodiment, the compound of the invention and at least one known cancer chemotherapeutic agent are administered substantially simultaneously, i.e. the compounds are administered at the same time or one after the

other, so long as the compounds reach therapeutic levels in the blood at the same time. On another embodiment, the compound of the invention and at least one known cancer chemotherapeutic agent are administered according to their individual dose schedule, so long as the compounds reach therapeutic levels in the blood.

[0090] It has been reported that alpha-1-adrenoceptor antagonists, such as doxazosin, terazosin, and tamsulosin can inhibit the growth of prostate cancer cell via induction of apoptosis (Kyprianou, N., *et al.*, *Cancer Res 60*:4550-4555, (2000)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known alpha-1-adrenoceptor antagonists, or a pharmaceutically acceptable salt of said agent. Examples of known alpha-1-adrenoceptor antagonists, which can be used for combination therapy include, but are not limited to, doxazosin, terazosin, and tamsulosin.

[0091] It has been reported that sigma-2 receptors are expressed in high densities in a variety of tumor cell types (Vilner, B. J., *et al.*, *Cancer Res. 55*: 408-413 (1995)) and that sigma-2 receptor agonists, such as CB-64D, CB-184 and haloperidol activate a novel apoptotic pathway and potentiate antineoplastic drugs in breast tumor cell lines. (Kyprianou, N., *et al.*, *Cancer Res. 62*:313-322 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known sigma-2 receptor agonist, or a pharmaceutically acceptable salt of said agonist. Examples of known sigma-2 receptor agonists which can be used for combination therapy include, but are not limited to, CB-64D, CB-184 and haloperidol.

[0092] It has been reported that combination therapy with lovastatin, a HMG-CoA reductase inhibitor, and butyrate, an inducer of apoptosis in the Lewis lung carcinoma model in mice, showed potentiating antitumor effects (Giermasz, A., *et al.*, *Int. J. Cancer 97*:746-750 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which

functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known HMG-CoA reductase inhibitor, or a pharmaceutically acceptable salt of said agent. Examples of known HMG-CoA reductase inhibitors, which can be used for combination therapy include, but are not limited to, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin.

[0093] It has been reported that HIV protease inhibitors, such as indinavir or saquinavir, have potent anti-angiogenic activities and promote regression of Kaposi sarcoma (Sgadari, C., *et al.*, *Nat. Med.* *8*:225-232 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known HIV protease inhibitor, or a pharmaceutically acceptable salt of said agent. Examples of known HIV protease inhibitors, which can be used for combination therapy include, but are not limited to, amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632.

[0094] It has been reported that synthetic retinoids, such as fenretinide (*N*-(4-hydroxyphenyl)retinamide, 4HPR), have good activity in combination with other chemotherapeutic agents, such as cisplatin, etoposide or paclitaxel in small-cell lung cancer cell lines (Kalemkerian, G. P., *et al.*, *Cancer Chemother. Pharmacol.* *43*:145-150 (1999)). 4HPR also was reported to have good activity in combination with gamma-radiation on bladder cancer cell lines (Zou, C., *et al.*, *Int. J. Oncol.* *13*:1037-1041 (1998)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known retinoid and synthetic retinoid, or a pharmaceutically acceptable salt of said agent. Examples of known retinoids and synthetic retinoids, which can be used for combination therapy include, but are not limited to, bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, fenretinide, and *N*-4-carboxyphenyl retinamide.

[0095] It has been reported that proteasome inhibitors, such as lactacystin, exert anti-tumor activity *in vivo* and in tumor cells *in vitro*, including those resistant to

conventional chemotherapeutic agents. By inhibiting NF-kappaB transcriptional activity, proteasome inhibitors may also prevent angiogenesis and metastasis *in vivo* and further increase the sensitivity of cancer cells to apoptosis (Almond, J. B., *et al., Leukemia 16*:433-443 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known proteasome inhibitor, or a pharmaceutically acceptable salt of said agent. Examples of known proteasome inhibitors, which can be used for combination therapy include, but are not limited to, lactacystin, MG-132, and PS-341.

[0096] It has been reported that tyrosine kinase inhibitors, such as STI571 (Imatinib mesilate, Gleevec®), have potent synergetic effect in combination with other anti-leukemic agents, such as etoposide (Liu, W.M., *et al. Br. J. Cancer 86*:1472-1478 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known tyrosine kinase inhibitor, or a pharmaceutically acceptable salt of said agent. Examples of known tyrosine kinase inhibitors, which can be used for combination therapy include, but are not limited to, Gleevec®, ZD1839 (Iressa), SH268, genistein, CEP2563, SU6668, SU11248, and EMD121974.

[0097] It has been reported that prenyl-protein transferase inhibitors, such as farnesyl protein transferase inhibitor R115777, possess preclinical antitumor activity against human breast cancer (Kelland, L.R., *et. al., Clin. Cancer Res. 7*:3544-3550 (2001)). Synergy of the protein farnesyltransferase inhibitor SCH66336 and cisplatin in human cancer cell lines also has been reported (Adjei, A. A., *et al., Clin. Cancer. Res. 7*:1438-1445 (2001)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known prenyl-protein transferase inhibitor, including farnesyl protein transferase inhibitor, inhibitors of geranylgeranyl-protein transferase type I

(GGPTase-I) and geranylgeranyl-protein transferase type-II, or a pharmaceutically acceptable salt of said agent. Examples of known prenyl-protein transferase inhibitors, which can be used for combination therapy include, but are not limited to, R115777, SCH66336, L-778,123, BAL9611 and TAN-1813.

[0098] It has been reported that cyclin-dependent kinase (CDK) inhibitors, such as flavopiridol, have potent synergetic effect in combination with other anticancer agents, such as CPT-11, a DNA topoisomerase I inhibitor in human colon cancer cells (Motwani, M., *et al.*, *Clin. Cancer Res. 7*:4209-4219, (2001)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known cyclin-dependent kinase inhibitor, or a pharmaceutically acceptable salt of said agent. Examples of known cyclin-dependent kinase inhibitor, which can be used for combination therapy include, but are not limited to, flavopiridol, UCN-01, roscovitine and olomoucine.

[0099] It has been reported that in preclinical studies COX-2 inhibitors were found to block angiogenesis, suppress solid tumor metastases, and slow the growth of implanted gastrointestinal cancer cells (Blanke, C. D., *Oncology (Huntingt) 16*(No. 4 Suppl. 3):17-21 (2002)). Therefore, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known COX-2 inhibitor, or a pharmaceutically acceptable salt of said inhibitor. Examples of known COX-2 inhibitors that can be used for combination therapy include, but are not limited to, celecoxib, valecoxib, and rofecoxib.

[00100] Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a bioconjugate of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in bioconjugation with at least one known therapeutically useful antibody, such as Herceptin® or Rituxan®, growth factors, such as DGF, NGF; cytokines, such as IL-2, IL-4, or any molecule that binds to the cell surface. The antibodies and other molecules will deliver a compound described herein to its targets and make it an

effective anticancer agent. The bioconjugates could also enhance the anticancer effect of therapeutically useful antibodies, such as Herceptin® or Rituxan®.

[00101] Similarly, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with radiation therapy. In this embodiment, the compound of the invention may be administered at the same time as the radiation therapy is administered or at a different time.

[00102] Yet another embodiment of the present invention is directed to a composition effective for post-surgical treatment of cancer, comprising a compound, or a pharmaceutically acceptable salt or prodrug of a compound described herein, which functions as a caspase cascade activator and inducer of apoptosis. The invention also relates to a method of treating cancer by surgically removing the cancer and then treating the animal with one of the pharmaceutical compositions described herein.

[00103] A wide range of immune mechanisms operates rapidly following exposure to an infectious agent. Depending on the type of infection, rapid clonal expansion of the T and B lymphocytes occurs to combat the infection. The elimination of the effector cells following an infection is one of the major mechanisms for maintaining immune homeostasis. The elimination of the effector cells has been shown to be regulated by apoptosis. Autoimmune diseases have lately been determined to occur as a consequence of deregulated cell death. In certain autoimmune diseases, the immune system directs its powerful cytotoxic effector mechanisms against specialized cells, such as oligodendrocytes in multiple sclerosis, the beta cells of the pancreas in diabetes mellitus, and thyrocytes in Hashimoto's thyroiditis (Ohsako, S. & Elkon, K.B., *Cell Death Differ.* *6*:13-21 (1999)). Mutations of the gene encoding the lymphocyte apoptosis receptor Fas/APO-1/CD95 are reported to be associated with defective lymphocyte apoptosis and autoimmune lymphoproliferative syndrome (ALPS), which is characterized by chronic, histologically benign splenomegaly, generalized lymphadenopathy, hypergammaglobulinemia, and autoantibody formation. (Infante, A.J., *et al.*, J. Pediatr. *133*:629-633 (1998) and Vaishnaw, A.K., *et al.*, J. Clin. Invest. *103*:355-363 (1999)). It was reported that overexpression of Bcl-2, which is a member of the bcl-2 gene family of programmed cell death regulators with

anti-apoptotic activity, in developing B cells of transgenic mice, in the presence of T cell dependent costimulatory signals, results in the generation of a modified B cell repertoire and in the production of pathogenic autoantibodies (Lopez-Hoyos, M., *et al.*, Int. J. Mol. Med. *1*:475-483 (1998)). It is therefore evident that many types of autoimmune disease are caused by defects of the apoptotic process. One treatment strategy for such diseases is to turn on apoptosis in the lymphocytes that are causing the autoimmune disease (O'Reilly, L.A. & Strasser, A., *Inflamm. Res. 48*:5-21 (1999)).

[00104] Fas-Fas ligand (FasL) interaction is known to be required for the maintenance of immune homeostasis. Experimental autoimmune thyroiditis (EAT), characterized by autoreactive T and B cell responses and a marked lymphocytic infiltration of the thyroid, is a good model to study the therapeutic effects of FasL. Batteux, F., *et al.*, (J. Immunol. *162*:603-608 (1999)) reported that by direct injection of DNA expression vectors encoding FasL into the inflamed thyroid, the development of lymphocytic infiltration of the thyroid was inhibited and induction of infiltrating T cells death was observed. These results show that FasL expression on thyrocytes may have a curative effect on ongoing EAT by inducing death of pathogenic autoreactive infiltrating T lymphocytes.

[00105] Bisindolylmaleimide VIII is known to potentiate Fas-mediated apoptosis in human astrocytoma 1321N1 cells and in Molt-4T cells; both of which were resistant to apoptosis induced by anti-Fas antibody in the absence of bisindolylmaleimide VIII. Potentiation of Fas-mediated apoptosis by bisindolylmaleimide VIII was reported to be selective for activated, rather than non-activated, T cells, and was Fas-dependent. Zhou T., *et al.*, (*Nat. Med. 5*:42-48 (1999)) reported that administration of bisindolylmaleimide VIII to rats during autoantigen stimulation prevented the development of symptoms of T cell-mediated autoimmune diseases in two models, the Lewis rat model of experimental allergic encephalitis and the Lewis adjuvant arthritis model. Therefore, the application of a Fas-dependent apoptosis enhancer, such as bisindolylmaleimide VIII, may be therapeutically useful for the more effective elimination of detrimental cells and inhibition of T cell-mediated autoimmune diseases. Therefore, an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis, is an effective treatment for autoimmune diseases.

[00106] Psoriasis is a chronic skin disease that is characterized by scaly red patches. Psoralen plus ultraviolet A (PUVA) is a widely used and effective treatment for psoriasis

vulgaris. Coven, *et al.*, Photodermatol. Photoimmunol. Photomed. *15*:22-27 (1999), reported that lymphocytes treated with psoralen 8-MOP or TMP and UVA, displayed DNA degradation patterns typical of apoptotic cell death. Ozawa, *et al.*, J. Exp. Med. *189*:711-718 (1999) reported that induction of T cell apoptosis could be the main mechanism by which 312-nm UVB resolves psoriasis skin lesions. Low doses of methotrexate may be used to treat psoriasis to restore a clinically normal skin. Heenen, *et al.*, Arch. Dermatol. Res. *290*:240-245 (1998), reported that low doses of methotrexate may induce apoptosis and that this mode of action could explain the reduction in epidermal hyperplasia during treatment of psoriasis with methotrexate. Therefore, an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis, is an effective treatment for hyperproliferative skin diseases, such as psoriasis.

[00107] Synovial cell hyperplasia is a characteristic of patients with rheumatoid arthritis (RA). It is believed that excessive proliferation of RA synovial cells, as well as defects in synovial cell death, may be responsible for synovial cell hyperplasia. Wakisaka, *et al.*, Clin. Exp. Immunol. 114:119-128 (1998), found that although RA synovial cells could die via apoptosis through a Fas/FasL pathway, apoptosis of synovial cells was inhibited by proinflammatory cytokines present within the synovium. Wakisaka, *et al.* also suggested that inhibition of apoptosis by the proinflammatory cytokines may contribute to the outgrowth of synovial cells, and lead to pannus formation and the destruction of joints in patients with RA. Therefore, an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis, is an effective treatment for rheumatoid arthritis.

[00108] There has been an accumulation of convincing evidence that apoptosis plays a major role in promoting resolution of the acute inflammatory response. Neutrophils are constitutively programmed to undergo apoptosis, thus limiting their pro-inflammatory potential and leading to rapid, specific, and non-phlogistic recognition by macrophages and semi-professional phagocytes (Savill, J., *J. Leukoc. Biol.* 61:375-380 (1997)). Boirivant, *et al.*, Gastroenterology *116*:557-565 (1999), reported that lamina propria T cells, isolated from areas of inflammation in Crohn's disease, ulcerative colitis, and other inflammatory states, manifest decreased CD2 pathway-induced apoptosis. In addition,

studies of cells from inflamed Crohn's disease tissue indicate that this defect is accompanied by elevated Bcl-2 levels. Therefore, an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of the compound of Formulae I-IV, which functions as a caspase cascade activator and inducer of apoptosis, is an effective treatment for inflammation.

[00109] Caspase cascade activators and inducers of apoptosis may also be a desirable therapy in the elimination of pathogens, such as HIV, Hepatitis C and other viral pathogens. The long lasting quiecence, followed by disease progression, may be explained by an anti-apoptotic mechanism of these pathogens leading to persistent cellular reservoirs of the virions. It has been reported that HIV-1infected T leukemia cells or peripheral blood mononuclear cells (PBMCs) underwent enhanced viral replication in the presence of the caspase inhibitor Z-VAD-fmk. Furthermore, Z-VAD-fmk also stimulated endogenous virus production in activated PBMCs derived from HIV-1-infected asymptomatic individuals (Chinnaiyan, A., *et al., Nat. Med. 3*:333 (1997)). Therefore, apoptosis serves as a beneficial host mechanism to limit the spread of HIV and new therapeutics using caspase/apoptosis activators are useful to clear viral reservoirs from the infected individuals. Similarly, HCV infection also triggers anti-apoptotic mechanisms to evade the host's immune surveillance leading to viral persistence and hepatocarcinogenesis (Tai, D.I., *et al. Hepatology 3*:656-64 (2000)). Therefore, apoptosis inducers are useful as therapeutics for HIV and other infectious disease.

[00110] Stent implantation has become the new standard angioplasty procedure. However, in-stent restenosis remains the major limitation of coronary stenting. New approaches have been developed to target pharmacological modulation of local vascular biology by local administration of drugs. This allows for drug applications at the precise site and time of vessel injury. Numerous pharmacological agents with antiproliferative properties are currently under clinical investigation, including actinomycin D, rapamycin or paclitaxel coated stents (Regar E., *et al., Br. Med. Bull.* 59:227-248 (2001)). Therefore, apoptosis inducers, which are antiproliferative, are useful as therapeutics for the prevention or reduction of in-stent restenosis.

[00111] Pharmaceutical compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount that is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the

skill of the art. Typically, the compounds may be administered to animals, e.g., mammals, orally at a dose of 0.0025 to 50 mg/kg of body weight, per day, or an equivalent amount of the pharmaceutically acceptable salt thereof, to a mammal being treated. Preferably, approximately 0.01 to approximately 10 mg/kg of body weight is orally administered. For intramuscular injection, the dose is generally approximately one-half of the oral dose. For example, a suitable intramuscular dose would be approximately 0.0025 to approximately 25 mg/kg of body weight, and most preferably, from approximately 0.01 to approximately 5 mg/kg of body weight. If a known cancer chemotherapeutic agent is also administered, it is administered in an amount that is effective to achieve its intended purpose. The amounts of such known cancer chemotherapeutic agents effective for cancer are well known to those skilled in the art.

[00112] The unit oral dose may comprise from approximately 0.01 to approximately 50 mg, preferably approximately 0.1 to approximately 10 mg of the compound of the invention. The unit dose may be administered one or more times daily, as one or more tablets, each containing from approximately 0.1 to approximately 10 mg, conveniently approximately 0.25 to 50 mg of the compound or its solvates.

[00113] In a topical formulation, the compound may be present at a concentration of approximately 0.01 to 100 mg per gram of carrier.

[00114] In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the compounds into preparations that may be used pharmaceutically. Preferably, the preparations, particularly those preparations which may be administered orally and that may be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations that may be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from approximately 0.01 to 99 percent, preferably from approximately 0.25 to 75 percent of active compound(s), together with the excipient.

[00115] Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic acid, such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid,

carbonic acid, phosphoric acid, oxalic acid, and the like. Basic salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic base, such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, Tris, *N*-methyl-glucamine and the like.

[00116] The pharmaceutical compositions of the invention may be administered to any animal, which may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans and veterinary animals, although the invention is not intended to be so limited.

[00117] The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, intrathecal, intracranial, intranasal or topical routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[00118] The pharmaceutical preparations of the present invention are manufactured in a manner, which is itself known, e.g., by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[00119] Suitable excipients are, in particular: fillers, such as saccharides, e.g. lactose or sucrose, mannitol or sorbitol; cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate; as well as binders, such as starch paste, using, e.g., maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, e.g., silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be

used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, e.g., for identification or in order to characterize combinations of active compound doses.

[00120] Other pharmaceutical preparations, which may be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active compounds in the form of: granules, which may be mixed with fillers, such as lactose; binders, such as starches; and/or lubricants, such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[00121] Possible pharmaceutical preparations, which may be used rectally include, e.g., suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, e.g., natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules, which consist of a combination of the active compounds with a base. Possible base materials include, e.g., liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

[00122] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, e.g., water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, e.g., sesame oil, or synthetic fatty acid esters, e.g., ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400), or cremophor, or cyclodextrins. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, e.g., sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[00123] In accordance with one aspect of the present invention, compounds of the invention are employed in topical and parenteral formulations and are used for the treatment of skin cancer.

[00124] The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included, as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in these topical formulations. Examples of such enhancers are found in U.S. Patent Nos. 3,989,816 and 4,444,762.

[00125] Creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture of the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. A typical example of such a cream is one which includes approximately 40 parts water, approximately 20 parts beeswax, approximately 40 parts mineral oil and approximately 1 part almond oil.

[00126] Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one that includes approximately 30 % almond oil and approximately 70 % white soft paraffin by weight.

[00127] The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00128] To an oven-dried carousel reaction flask charged with a magnetic stir bar at room temperature (rt) under argon was added 4-chloro-2-methylthieno[3,2-*d*]pyrimidine (0.100 g, 0.541 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and 2.0 M HCl in ether (0.250 mL). The orange suspension was heated at 80°C for 4 h, cooled to rt and diluted with H_2O (2 mL). The organic solvent was removed by rotary evaporation and the aqueous layer was neutralized to pH = 7 by the addition of saturated $NaHCO_3$(aq). The resulting precipitate was filtered and collected to give 0.084 g (51%)

of the title compound as a green solid. ^{1}H NMR ($CDCl_3$) 8.39 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 5.2 Hz, 1H), 7.40 (d, J = 5.5 Hz, 1H), 7.34 (br s, 1H), 6.86 (d, J = 9.1 Hz, 1H), 6.62 (dd, J = 9.1 and 2.5 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 2.74 (s, 3H).

EXAMPLE 2

N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00129] The title compound was prepared in a manner similar example 1. From 4-chlorothieno[3,2-*d*]pyrimidine (0.092 g, 0.54 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and 2.0 M HCl in ether (0.250 mL) was obtained 0.070 g (45%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.78 (s, 1H), 8.31 (d, J = 3.0 Hz, 1H), 7.78 (d, J = 5.2 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 7.37 (br s, 1H), 6.87 (d, J = 9.1 Hz, 1H), 6.63 (dd, J = 9.1 and 2.8 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H).

EXAMPLE 3

N-(2,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine

[00130] The title compound was prepared in a manner similar example 1. From 4-chloro-2-methylthieno[2,3-*d*]pyrimidine (0.100 g, 0.541 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and concentrated HCl (5 drops) was obtained 0.005 g (3%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) 8.60 (d, J = 3.3 Hz, 1H), 7.74 (br s, 1H), 7.30-7.25 (m, 2H), 6.86 (d, J = 9.1 Hz, 1H), 6.58 (dd, J = 8.5 and 3.0 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.73 (s, 3H).

EXAMPLE 4

N-(2-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00131] The title compound was prepared in a manner similar to example 1. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), o-anisidine (0.073 mL, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.076 g (50%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.77 (s, 1H), 8.45 (dd, J

= 7.8 and 1.8 Hz, 1H), 7.76 (d, J =5.5 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.30 (br s, 1H), 7.17-7.03 (m, 2H), 6.97 (dd, J = 8.0 and 1.7 Hz, 1H), 3.94 (s, 3H).

EXAMPLE 5

N-(2,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00132] To an oven-dried carousel reaction flask charged with a magnetic stir bar at rt under argon was added 4-chlorothieno[2,3-*d*]pyrimidine (0.092 g, 0.54 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and 2.0 M HCl in ether (0.250 mL). The yellow suspension was heated at 80°C for 1 h and then cooled to rt. The resulting precipitate was filtered and dried to give 0.15 g (87%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 9.87 (br s, 1H), 8.46 (s, 1H), 7.85 (d, J = 6.1 Hz, 1H), 7.77 (d, J = 5.8 Hz, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.08 (d, J = 9.1 Hz, 1H), 6.87 (dd, J = 9.1 and 3.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H).

EXAMPLE 6

N-(2,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00133] The title compound was prepared in a manner similar to example 5. From 4-chloro-5-methylthieno[2,3-*d*]pyrimidine (0.100 g, 0.541 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and 2.0 M HCl in ether (0.250 mL) was obtained 0.15 g (81%) of the title compound as a green solid. ^{1}H NMR (DMSO-d_6) 8.58 (s, 1H), 8.54 (br s, 1H), 8.24 (d, J = 3.0 Hz, 1H), 7.42 (d, J = 1.1 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.68 (dd, J = 9.0 and 3.1 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 2.75 (s, 3H).

EXAMPLE 7

N-(2,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00134] The title compound was prepared in a manner similar to example 5. From 4-chloro-2,5-dimethylthieno[2,3-*d*]pyrimidine (0.107 g, 0.541 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and concentrated HCl (5 drops) was obtained 0.14 g (79%) of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$) 8.99 (br

s, 1H), 8.41 (d, J = 2.8 Hz, 1H), 7.14 (s, 1H), 6.92 (d, J = 9.1 Hz, 1H), 6.74 (dd, J = 9.1 and 3.0 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H), 2.96 (s, 3H), 2.79 (s, 3H).

EXAMPLE 8

N-(2,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00135] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), 2,4-dimethoxyaniline (0.099 g, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.14 g (75%) of the title compound as a gray solid. ^{1}H NMR (DMSO-d_6) 11.81 (br s, 1H), 8.87 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 7.58 (d, J = 5.5 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.66 (dd, J = 8.7 and 2.6 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H).

EXAMPLE 9

N-(2,3-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00136] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), 2,3-dimethoxyaniline (0.099 g, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.16 g (83%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 11.19 (br s, 1H), 8.85 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 7.54 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 4.9 Hz, 2H), 7.06-7.02 (m, 1H), 3.88 (s, 3H), 3.68 (s, 3H).

EXAMPLE 10

N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00137] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), 3,4,5-trimethoxyaniline (0.118 g, 0.650 mmol) and concentrated HCl (5 drops) was obtained 0.183 g (88%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 11.21 (s, 1H), 8.90 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 7.56 (dd, J = 5.5 and 1.1 Hz, 1H), 7.06 (s, 2H), 3.79 (s, 6H), 3.71 (s, 3H).

EXAMPLE 11

N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00138] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), m-anisidine (0.072 mL, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.15 g (86%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 10.88 (br s, 1H), 8.85 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.40-7.30 (m, 3H), 6.88 (d, J = 9.1 Hz, 1H), 3.79 (s, 3H).

EXAMPLE 12

N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00139] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), 3,5-dimethoxyaniline (0.099 g, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.13 g (71%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 11.04 (br s, 1H), 8.90 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 6.96 (d, J = 2.2 Hz, 2H), 6.47 (t, J = 2.2 Hz, 1H), 3.77 (s, 6H).

EXAMPLE 13

N-(4-Methoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00140] The title compound was prepared in a manner similar to example 5. From 4-chloro-2,5-dimethylthieno[2,3-*d*]pyrimidine (0.054 g, 0.27 mmol), isopropanol (1.4 mL), p-anisidine (0.037 g, 0.30 mmol) and concentrated HCl (3 drops) was obtained 0.052 g (60%) of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6) 8.71 (br s, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.30 (s, 1H), 6.99 (d, J = 9.1 Hz, 2H), 3.78 (s, 3H), 2.71 (s, 3H), 2.48 (s, 3H).

EXAMPLE 14

N-(3,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00141] The title compound was prepared in a manner similar to example 5. From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), 3,4-dimethoxyaniline (0.099 g, 0.65 mmol) and concentrated HCl (5 drops) was obtained 0.15 g (78%) of the title compound as a green solid. ^{1}H NMR (DMSO-d_6) 11.31 (br s, 1H), 8.88 9s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H).

EXAMPLE 15

N-(4-Methoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine

[00142] To an oven-dried carousel reaction flask charged with a magnetic stir bar at rt under argon was added 4-chloro-2-methylthieno[2,3-*d*]pyrimidine (0.050 g, 0.27 mmol), isopropanol (1.4 mL), p-anisidine (0.037 g, 0.30 mmol) and concentrated HCl (3 drops). The brown suspension was heated at 80°C for 2 h, and then cooled to rt. The resulting precipitate was filtered and collected to give the crude product. Purification by flash column chromatography (silica gel 12 g pre-packed column, elution with EtOAc:Hexanes, 1:2) gave 0.004 g (5%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 9.42 (br s, 1H), 7.76-7.70 (m, 3H), 7.55 (d, J = 6.0 Hz, 1H), 6.97-6.94 (m, 2H), 3.76 (s, 3H), 2.48 (s, 3H).

EXAMPLE 16

N-(2,5-Dimethoxyphenyl)-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00143] To a mixture of 4-chloro-5-methyl-6-phenylthieno[2,3-*d*]pyrimidine (100 mg, 0.38 mmol) and 2,5-dimethoxybenzenamine (65 mg, 0.42 mmol) in 2.5 mL of isopropanol was added 2 drops of concentrated HCl and the mixture was heated at 75 °C for 3 h. The precipitated product was collected by filtration, washed with cold isopropanol and dried under vacuum to give the title compound (103 mg, 0.25 mmol, 66%). ^{1}H NMR (DMSO-d_6) 8.61 (s, 1H, broad), 8.59 (s, 1H), 8.25 (d, 1H, J = 3.0), 7.48

– 7.57 (m, 5H), 7.04 (d, 1H, J = 9.3), 6.68 (dd, 1H, J = 9.0, 3.0), 3.86 (s, 3H), 3.76 (s, 3H), 2.72 (s, 3H).

EXAMPLE 17

6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00144] The title compound was prepared from 4-chloro-6-iodothieno[3,2-*d*]pyrimidine and 2,5-dimethoxybenzenamine in a manner similar example 16. ^{1}H NMR (DMSO-d_6) 8.76 (s, 1H), 7.80 (s, 1H), 7.05 – 7.18 (m, 3H), 3.75 (s, 3H), 3.69 (s, 3H).

EXAMPLE 18

6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00145] The title compound was prepared from 4-chloro-6-iodo-7-methylthieno[3,2-*d*]pyrimidine and 2,5-dimethoxybenzenamine in a manner similar example 16. ^{1}H NMR (DMSO-d_6) 8.68 (s, 1H), 7.13 – 7.16 (m, 1H), 7.02 – 7.05 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 2.35 (s, 3H).

EXAMPLE 19

N-(4-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00146] The title compound was prepared from 4-chloro-thieno[3,2-*d*]pyrimidine and 4-methoxybenzenamine in a manner similar example 16. ^{1}H NMR (DMSO-d_6) 8.88 (s, 1H), 8.47 (d, 1H, J = 5.4), 7.52 – 7.59 (m, 3H), 7.03 – 7.08 (m, 2H), 3.81 (s, 3H).

EXAMPLE 20

6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00147] To a mixture of 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine (96 mg, 0.38 mmol) and 2,5-dimethoxybenzenamine (65 mg, 0.42 mmol) in 2.5 mL of isopropanol was added 2 drops of concentrated HCl and the mixture was heated at 75 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with 25 mL of ethyl acetate, and

washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (40% ethyl acetate/hexane) to give the title compound (116 mg, 0.32 mmol, 84%). ^1H NMR ($CDCl_3$) 8.70 (s, 1H), 8.07 (d, 1H, $J = 3.0$), 7.45 (s, 1H), 7.18 (s, 1H, broad), 6.87 (d, 1H, $J = 8.7$), 6.67 (dd, 1H, $J = 9.0$, 3.0), 3.88 (s, 3H), 3.83 (s, 3H).

EXAMPLE 21

N-(5-Methylisoxazol-3-yl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00148] The title compound was prepared from 4-chloro-thieno[3,2-*d*]pyrimidine and 5-methylisoxazol-3-amine in a manner similar example 16. ^1H NMR (DMSO-d_6) 8.94 (s, 1H), 8.52 (d, 1H, $J = 5.4$), 7.63 (d, 1H, $J = 5.4$), 6.90 (m, 1H), 2.46 (d, 3H, $J = 0.9$).

EXAMPLE 22

N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine

[00149] The title compound was prepared from 4-chloro-7-methylthieno[3,2-*d*]pyrimidine and 2,5-dimethoxybenzenamine in a manner similar example 20. ^1H NMR ($CDCl_3$) 8.83 (s, 1H), 8.36 (d, 1H, $J = 3.3$), 7.40 (m, 1H), 7.34 (s, broad, 1H), 6.85 (d, 1H, $J = 9.0$), 6.61 (dd, 1H, $J = 9.0$, 3.0), 3.91 (s, 3H), 3.84 (s, 3H), 2.5 (d, 3H, $J = 1.2$).

EXAMPLE 23

N-(4-Methoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine

[00150] The title compound was prepared in a manner similar to Example 20 from 4-methoxyaniline and 4-chloro-5-methylthieno[2,3-*d*]pyrimidine. ^1H NMR ($CDCl_3$) 8.49 (s, 1H), 7.48 – 7.52 (m, 2H), 7.12 (s, broad, 1H), 6.93 – 6.97 (m, 3H), 3.83 (s, 3H), 2.74 (d, 3H, $J = 0.9$).

EXAMPLE 24

N-(1*H*-Indol-5-yl)thieno[3,2-*d*]pyrimidin-4-amine

[00151] The title compound was prepared from 4-chlorothieno[3,2-*d*]pyrimidine and 1*H*-indol-5-amine in a manner similar to example 1. ^{1}H NMR (DMSO-d_6) 11.15 (s, broad, 1H), 9.57 (s, 1H), 8.48 (s, 1H), 8.06 (d, 1H, J = 5.7 Hz), 7.76 (d, 1H, J = 1.5 Hz), 7.34 – 7.42 (m, 3H), 7.23 (dd, 1H, J = 8.7 and 2.1 Hz), 6.45 (m, 1H).

EXAMPLE 25

N-(3-Bromophenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00152] The title compound was prepared from 4-chloro-thieno[3,2-*d*]pyrimidine and 3-bromoaniline in a manner similar to example 5. ^{1}H NMR (DMSO-d_6) 8.95 (s, 1H), 8.53 (d, 1H, J = 5.7 Hz), 8.07 (t, 1H, J = 2.1 Hz), 7.76 (dt, 1H, J = 8 and 2.1 Hz), 7.61 (d, 1H, J = 5.4 Hz), 7.34 – 7.50 (m, 2H).

EXAMPLE 26

N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine

[00153] The title compound was prepared from 4-chloro-2-phenylthieno[3,2-*d*]pyrimidine and 2,5-dimethoxyaniline in a manner similar to example 20. ^{1}H NMR ($CDCl_3$) 8.60 (d, 1H, J = 3.0 Hz), 8.53 – 8.56 (m, 2H), 7.78 (d, 1H, J = 5.1 Hz), 7.46 – 7.56 (m, 5H), 6.88 (d, 1H, J = 8.7 Hz), 6.63 (dd, 1H, J = 9.0 and 3.0 Hz), 3.93 (s, 3H), 3.90 (s, 3H).

EXAMPLE 27

N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine

[00154] The title compound was prepared from 4-chloro-2-(methylthio)thieno[3,2-*d*]pyrimidine and 2,5-dimethoxyaniline in a manner similar to example 20. ^{1}H NMR ($CDCl_3$) 8.29 (d, 1H, J = 3.0 Hz), 7.71 (d, 1H, J = 5.1 Hz), 7.36 (s, broad, 1H), 7.33 (d, 1H, J = 5.1 Hz), 6.85 (d, 1H, J = 8.7 Hz), 6.61 (dd, 1H, J = 8.7 and 3.0 Hz), 3.91 (s, 3H), 3.83 (s, 3H), 2.68 (s, 3H).

EXAMPLE 28

N-(2,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00155] The title compound was prepared in a manner similar to example 5. From 4-chloro-6-methylthieno[2,3-*d*]pyrimidine (0.100 g, 0.542 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and concentrated HCl (5 drops) was obtained 0.131 g (71%) of the title compound as a brown solid. ^{1}H NMR (DMSO-d_6) 9.84 (br s, 1H), 8.43 (d, J = 2.2 Hz, 1H), 7.56 (s, 1H), 7.27 (d, J = 3.0 Hz, 1H), 7.08 (d, J = 9.1 Hz, 1H), 6.87 (dd, J = 9.1 and 3.0 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.60 (s, 3H).

EXAMPLE 29

N-(2,5-Dimethoxy-phenyl)-2,5,6-trimethylthieno[2,3-*d*]pyrimidin-4-amine hydrochloride

[00156] The title compound was prepared in a manner similar to example 5. From 4-chloro-2,5,6-trimethylthieno[2,3-*d*]pyrimidine (0.115 g, 0.542 mmol), isopropanol (2.7 mL), 2,5-dimethoxyaniline (0.091 g, 0.59 mmol) and 2.0M HCl in ether (0.250 mL) was obtained 0.120 g (67%) of the title compound as a green solid. ^{1}H NMR (DMSO-d_6) 8.60 (br s, 1H), 8.30 (d, J = 3.0 Hz, 1H), 7.05 (d, J = 9.3 Hz, 1H), 6.67 (dd, J = 9.3 and 3.0 Hz, 1Hz), 3.87 (s, 3H), 3.76 (s, 3H), 2.59 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H).

EXAMPLE 30

N-(2-Methoxy-6-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00157] The title compound was prepared from 4-chlorothieno[3,2-*d*]pyrimidine and 2-methoxy-6-methylaniline in a manner similar example 3. ^{1}H NMR ($CDCl_3$) 8.59 (s, 1H), 7.57 (d, 1H, J = 5.4 Hz), 7.27 – 7.35 (m, 2H), 6.93 (d, 1H, J = 7.8 Hz), 6.83 (d, 1H, J = 8.4 Hz), 3.71 (s, 3H), 2.26 (s, 3H).

EXAMPLE 31

N-(2-Methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00158] The title compound was prepared from 4-chlorothieno[3,2-*d*]pyrimidine and 2-methoxy-5-methylaniline in a manner similar example 3. ^{1}H NMR ($CDCl_3$) 8.60 (s,

1H), 7.96 (d, broad, 1H), 7.64 (d, 1H, J = 5.4 Hz), 7.36 (d, 1H, J = 5.4 Hz), 7.22 (d, 1H, J = 8.4 Hz), 7.07 (d, 1H, J = 2.7 Hz), 6.89 (dd, 1H, J = 8.4 and 2.7 Hz), 3.8 (s, 3H), 2.22 (s, 3H).

EXAMPLE 32

N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine

[00159] A mixture of 6-bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine (59 mg, 0.16 mmol) and phenylboronic acid (40 mg, 0.33 mmol) in 2 mL of dimethylformamide was stirred with Argon passing it for 2 min. To the mixture was added bis(benzonitrile)palladium(II)chloride (6 mg, 0.016 mmol), 1,1`-bis(diphenylphosphino)-ferrocene (18 mg, 0.032 mmol) and sodium carbonate (1M, 0.35 mL, 0.35 mmol), Argon was passed through the mixture for 2 min and the mixture was heated overnight at 80°C. The reaction mixture was cooled to room temperature, diluted with 25 mL of ethyl acetate and washed with water (15 mL x 3) and saturated sodium chloride. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (35% ethyl acetate/hexanes) to give the title compound (56 mg, 0.15 mmol, 96%). ^{1}H NMR ($CDCl_3$): 8.77 (s, 1H), 8.34 (d, 1H, J = 3.0 Hz) 7.77 (m, 1H), 7.74 (m, 1H), 7.65 (s, 1H), 7.42 – 7.51 (m, 3H), 7.35 (s, broad, 1H), 6.87 (d, 1H, J = 8.7 Hz), 6.62 (dd, 1H, J = 8.7 and 3.0 Hz), 3.93 (s, 3H), 3.85 (s, 3H).

EXAMPLE 33

3-[4-(Thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl]acrylic acid ethyl ester

[0001] To an oven-dried carousel reaction flask charged with a magnetic stir bar at rt under argon was added 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol), isopropanol (2.9 mL), ethyl 4-aminocinnamate (0.123 g, 0.645 mmol) and concentrated HCl (5 drops). The brown suspension was heated at 80°C for 3.5 h, and then cooled to rt. The resulting precipitate was filtered and collected to give 0.174 g (82%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 11.28 (br s, 1H), 8.92 (d, J = 1.1 Hz, 1H), 8.52 (dd, J = 5.4 and 1.2 Hz, 1H), 7.87-7.78 (m, 4H), 7.67 (d, J = 15.9 Hz, 1H), 7.61

(dd, J = 5.5 and 1.4 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H).

Compounds of EXAMPLE 34-65 were prepared by a procedure similar to that of Example 33.

EXAMPLE 34

N-(2,5-Dimethoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine

[00160] From 4-chloro-5,6-dimethylthieno[2,3-*d*]pyrimidine (0.108 g, 0.542 mmol) and 2,5-dimethoxyaniline (0.091 g, 0.60 mmol) was obtained 0.008 g (5%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.58 (d, J = 3.0 Hz, 1H), 8.55 (s, 1H), 8.31 (br s, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.55 (dd, J = 8.8 and 3.0 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.63 (s, 3H), 2.48 (s, 3H).

EXAMPLE 35

N-(5-Methoxy-2-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00161] From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol) and 5-methoxy-2-nitroaniline (0.108 mL, 0.645 mmol) was obtained 0.005 g (3%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 11.19 (br s, 1H), 9.02 (d, J = 2.8 Hz, 1H), 8.91 (s, 1H), 8.31 (d, J = 9.3 Hz, 1H), 7.93 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 6.68 (dd, J = 9.6 and 2.8 Hz, 1H), 4.01 (s, 3H).

EXAMPLE 36

N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00162] From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol) and 2,5-diethoxyaniline (0.117 mL, 0.645 mmol) was obtained 0.115 g (62%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.80 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 8.8 and 3.0 Hz, 1H), 4.14-4.03 (m, 4H), 1.50-1.42 (m, 6H).

EXAMPLE 37

N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00163] From 4-chlorothieno[3,2-*d*]pyrimidine (0.075 g, 0.44 mmol) and 2-methoxy-5-nitroaniline (0.081 g, 0.48 mmol) was obtained 0.029 g (22%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) 9.72 (d, J = 2.8 Hz, 1H), 8.91 (s, 1H), 8.04 (dd, J = 8.8 and 2.8 Hz, 1H), 7.85 (d, J = 5.5 Hz, 1H), 7.55 (d, J = 5.5, 1H), 7.38 (br s, 1H), 7.02 (d, J = 9.1 Hz, 1H), 4.11 (s, 3H)

EXAMPLE 38

N-(2-Methoxy-5-phenoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00164] From 4-chlorothieno[3,2-*d*]pyrimidine (0.075 g, 0.44 mmol) and 5-phenoxy-*o*-anisidine (0.104 mL, 0.483 mmol) was obtained 0.031 g (20%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.72 (s, 1H), 8.48 (d, J = 3.0 Hz, 1H), 7.77 (dd, J = 5.2 and 0.6 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H), 7.42 (br s, 1H), 7.35-7.30 (m, 2H), 7.09-7.01 (m, 3H), 6.89 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.8 and 2.7 Hz, 1H), 3.95 (s, 3H).

EXAMPLE 39

N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00165] From 4-chlorothieno[3,2-*d*]pyrimidine (0.075 g, 0.44 mmol) and 5-chloro-*o*-anisidine (0.076 mL, 0.48 mmol) was obtained 0.021 g (16%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) 8.83 (s, 1H), 8.76 (d, J = 2.5 Hz, 1H), 7.80 (d, J = 5.5 Hz, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.34 (br s, 1H), 7.05 (dd, J = 8.8 and 2.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H).

EXAMPLE 40

N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00166] From 4-chlorothieno[3,2-*d*]pyrimidine (0.075 g, 0.44 mmol) and 5-*tert*-butyl-*o*-anisidine (0.087 mL, 0.48 mmol) was obtained 0.060 g (44%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.75 (s, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.71 (d, J = 5.5 Hz,

1H), 7.44-7.43 (m, 2H), 7.19 (dd, J = 8.7 and 2.3 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 1.36 (s, 9H).

EXAMPLE 41

4-Methoxy-3-(thieno[3,2-*d*]pyrimidin-4-ylamino)-benzoic acid

[00167] From 4-chlorothieno[3,2-*d*]pyrimidine (0.075 g, 0.44 mmol) and 3-amino-4-methoxybenzoic acid (0.059 g, 0.35 mmol) was obtained 0.025 g (24%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 11.09 (br s, 1H), 8.84 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.04 (dd, J = 8.7 and 2.1 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.54 (d, J = 5.5, 1H), 7.33 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H)

EXAMPLE 42

N-(2-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00168] From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol) and 2-hydroxy-5-methoxyaniline (0.090 g, 0.64 mmol) was obtained 0.106 g (59%) of the title compound as a gray solid. ^{1}H NMR (DMSO-d_6) 11.04 (br s, 1H), 9.57 (br s, 1H), 8.56 (s, 1H), 8.41 (d, J = 5.5 Hz, 1H), 7.51 (d, J = 5.5 Hz, 1H), 6.99-6.91 (m, 3H), 3.70 (s, 3H).

EXAMPLE 43

N-(3,5-Dihydroxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00169] From 4-chlorothieno[3,2-*d*]pyrimidine (0.118 g, 0.690 mmol) and 5-aminobenzene-1,3-diol (0.095 g, 0.76 mmol) was obtained 0.006 g (3%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 9.45 (s, 1H), 9.26 (s, 2H), 8.56 (s, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.44 (d, J = 5.2 Hz, 1H), 6.72 (d, J = 1.9 Hz, 2H), 6.00 (d, J = 1.9 Hz, 1H).

EXAMPLE 44

N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00170] From 4-chlorothieno[3,2-*d*]pyrimidine (0.100 g, 0.586 mmol) and 3-amino-5-methoxyphenol (0.090 mL, 0.65 mmol) was obtained 0.031 g (19%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 9.54 (s, 1H), 9.46 (s, 1H), 8.59 (s, 1H), 8.22 (d, J = 5.5 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 6.11 (s, 1H), 3.71 (s, 3H).

EXAMPLE 45

N-(3,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine

[00171] From 4-chlorothieno[2,3-*d*]pyrimidine (0.250 g, 1.46 mmol) and 3,5-dimethoxyaniline (0.246 g, 1.61 mmol) was obtained 0.403 g (85%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 9.91 (br s, 1H), 8.58 (s, 1H), 7.98 (d, J = 5.8 Hz, 1H), 7.78 (d, J = 6.0 Hz, 1H), 7.16 (d, J = 2.2 Hz, 2H), 6.31 (t, J = 2.2, 1H), 3.77 (s, 6H).

EXAMPLE 46

N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine

[00172] From 4-chloro-7-methylthieno[3,2-*d*]pyrimidine (0.100 g, 0.542 mmol) and 3,5-dimethoxyaniline (0.083 g, 0.54 mmol) was obtained 0.105 g (57%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 10.95 (br s, 1H), 8.87 (s, 1H), 8.12 (s, 1H), 6.98 (s, 2H), 6.45 (s, 1H), 3.77 (s, 6H), 2.44 (s, 3H).

EXAMPLE 47

N-(3,5-Dimethoxyphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-amine

[00173] From 4-chloro-5,6-dimethylthieno[2,3-*d*]pyrimidine (0.100 g, 0.503 mmol) and 3,5-dimethoxyaniline (0.077 g, 0.50 mmol) was obtained 0.104 g (59%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 8.54 (br s, 1H), 8.48 (s, 1H), 6.93 (d, J = 2.2 Hz, 2H), 6.31 (t, J = 2.2 Hz, 1H), 3.75 (s, 6H), 2.59 (s, 3H), 2.47 (s, 3H).

EXAMPLE 48

N-(3,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine

[00174] From 4-chloro-6-methylthieno[2,3-*d*]pyrimidine (0.100 g, 0.542 mmol) and 3,5-dimethoxyaniline (0.083 g, 0.54 mmol) was obtained 0.150 g (82%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 9.73 (br s, 1H), 8.52 (s, 1H), 7.65 (d, J = 1.4 Hz, 1H), 7.15 (d, J = 2.5 Hz, 2H), 6.29 (t, J = 2.2 Hz, 1H), 3.76 (s, 6H), 2.60 (s, 3H).

EXAMPLE 49

N-(3,5-Dimethoxyphenyl)-5-methyl-6-phenylthieno[2,3-*d*]pyrimidin-4-amine

[00175] From 4-chloro-5-methyl-6-phenylthieno[2,3-*d*]pyrimidine (0.100 g, 0.383 mmol) and 3,5-dimethoxyaniline (0.059 g, 0.38 mmol) was obtained 0.003 g (2%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.58 (s, 1H), 7.50-7.46 (m, 5H), 7.36 (br s, 1H), 6.93 (d, J = 2.2 Hz, 2H), 6.29 (t, J = 2.2 Hz, 1H), 3.84 (s, 6H), 2.72 (s, 3H).

EXAMPLE 50

N-(3,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine

[00176] From 4-chloro-5-methylthieno[2,3-*d*]pyrimidine (0.035 g, 0.19 mmol) and 3,5-dimethoxyaniline (0.029 g, 0.19 mmol) was obtained 0.037 g (58%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 8.49 (s, 1H), 8.32 (br s, 1H), 7.35 (s, 1H), 6.96 (d, J = 2.2 Hz, 2H), 6.30 (t, J = 2.0 Hz, 1H), 3.75 (s, 6H), 2.73 (s, 3H).

EXAMPLE 51

N-(3,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine

[00177] From 4-chloro-2,5-dimethylthieno[2,3-*d*]pyrimidine (0.105 g, 0.528 mmol) and 3,5-dimethoxyaniline (0.081 g, 0.53 mmol) was obtained 0.124 g (56%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 8.41 (br s, 1H), 7.27 (d, J = 1.1 Hz, 1H), 7.03 (d, J = 2.2 Hz, 2H), 6.30 (t, J = 2.2 Hz, 1H), 3.76 (s, 6H), 2.71 (s, 3H), 2.53 (s, 3H).

EXAMPLE 52

N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00178] From 6-bromo-4-chloro-2-methylthieno[3,2-*d*]pyrimidine (0.105 g, 0.398 mmol), and 3,5-dimethoxyaniline (0.061 g, 0.40 mmol) was obtained 0.125 g (82%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 7.64 (s, 1H), 7.02 (s, 2H), 6.37 (s, 1H), 3.76 (s, 6H), 2.56 (s, 3H).

EXAMPLE 53

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine

[00179] From 4-chloro-6-iodothieno[3,2-*d*]pyrimidine (0.126 g, 0.404 mmol) and 3,5-dimethoxyaniline (0.062 g, 0.40 mmol) was obtained 0.025 g (14%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.59 (s, 1H), 7.62 (s, 1H), 7.17 (br s, 1H), 6.66 (d, J = 2.2 Hz, 2H), 6.43 (t, J = 2.2 Hz, 1H), 3.82 (s, 6H).

EXAMPLE 54

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00180] From 4-chloro-2-methylthieno[3,2-*d*]pyrimidine (0.250 g, 1.35 mmol) and 3,5-dimethoxyaniline (0.207 g, 1.35 mmol) was obtained 0.266 g (58%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 11.27 (br s, 1H), 8.49 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.5 Hz, 1H), 6.98 (s, 2H), 6.49 (s, 1H), 3.78 (s, 6H), 2.68 (s, 3H).

EXAMPLE 55

N-(3,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine

[00181] From 4-chloro-2-methylthieno[2,3-*d*]pyrimidine (0.165 g, 0.893 mmol) and 3,5-dimethoxyaniline (0.137 g, 0.893 mmol) was obtained 0.275 g (91%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 9.76 (m, 1H), 7.89 (d, J = 6.2 Hz, 1H), 7.66 (d, J = 5.9 Hz, 1H), 7.22 (d, J = 2.2 Hz, 2H), 6.28 (t, J = 2.2 Hz, 1H), 3.77 (s, 6H), 2.57 (s, 3H).

EXAMPLE 56

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00182] From 4-chlorothieno[3,2-*d*]pyrimidine (0.689 g, 4.05 mmol) and 5-methoxy-3-trifluoromethylbenzenamine (0.773 g, 4.05 mmol) was obtained 1.34 g (92%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 8.90 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 7.69 (brs, 1H), 7.61 (brs, 1H), 7.58 (d, J = 5.7 Hz, 1H), 7.19 (brs, 1H), 3.94 (s, 3H).

EXAMPLE 57

N-(3,5-Dimethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00183] From 4-chlorothieno[3,2-*d*]pyrimidine (689 mg, 4.05 mmol) and 3,5-dimethylbenzenamine (490 mg, 4.05 mmol) was obtained 830 mg (70%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 8.76 (s, 1H), 8.38 (d, J = 5.1 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 7.22 (brs, 2H), 7.11(brs, 1H), 2.37 (s, 6H).

EXAMPLE 58

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate

[00184] From 4-chlorothieno[3,2-d]pyrimidine (0.689 g, 4.05 mmol) and dimethyl 5-aminobenzene-1,3-dioate (0.846 g, 4.05 mmol) was obtained 1.31 g (85%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) 11.08 (s, 1H), 8.93 (s, 1H), 8.73 (s, 2H), 8.49 (d, J = 5.4 Hz, 1H), 8.29 (s, 1H), 7.60 (d, J = 5.4 Hz, 1H), 3.93 (s, 6H).

EXAMPLE 59

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00185] From 4-chlorothieno[3,2-*d*]pyrimidine (1.23 g, 7.23 mmol) and 3-methoxy-5-nitrobenzenamine (1.22 g, 7.23 mmol) was obtained 2.28 g (93%) of the title compound as a solid. ^{1}H NMR ($CDCl_3$) 8.93 (s, 1H), 8.52 (d, J = 5.4 Hz, 1H), 8.35 (brs, 1H), 7.78 (t, J = 2.1 Hz, 1H), 7.74 (t, J = 2.1 Hz, 1H), 7.59 (d, J = 5.7Hz, 1H), 3.96 (s, 3H).

EXAMPLE 60

N-(3,5-Bis(methylsulfonyl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00186] From 4-chlorothieno[3,2-*d*]pyrimidine (341 mg, 2 mmol), and 3,5-bis(methylsulfonyl)benzenamine (498 mg, 2 mmol) was obtained 830 mg (99%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 9.01 (s, 1H), 8.77 (s, 2H), 8.58 (d, J = 5.4 Hz, 1H), 8.39 (brs, 1H), 7.63 (d, J = 5.4 Hz, 1H), 3.31 (s, 6H).

EXAMPLE 61

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00187] From 4-chlorothieno[3,2-*d*]pyrimidine (240 mg, 1.41 mmol), and 3-methoxy-5-(1*H*-tetrazol-1-yl)benzenamine (248 mg, 1.41 mmol) was obtained 418 mg (82%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 9.83 (s, 1H), 8.89 (s, 1H), 8.48 (d, J = 5.7 Hz, 1H), 8.02 (bs, 1H), 7.57 (d, J = 5.7Hz, 1H), 7.53 (t, J = 2.1Hz, 1H), 7.44 (t, J = 5.7Hz, 1H), 3.96 (s, 6H).

EXAMPLE 62

N-(2,6-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00188] From 4-chlorothieno[3,2-*d*]pyrimidine (104 mg, 0.612 mmol) and 2,6-dimethoxyaniline (121 mg, 0.79 mmol) was obtained 117 mg (67%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) 10.90 (s, 1H), 8.85 (s, 1H), 8.39 (m, 1H), 7.49 (m, 2H), 6.85 (d, 2H, J = 8.4 Hz), 3.73 (s, 6H).

EXAMPLE 63

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00189] From 4-chloro-2-methylthieno[3,2-*d*]pyrimidine (31 mg, 0.17 mmol) and 5-methoxy-*N*1,*N*1-dimethylbenzene-1,3-diamine (34 mg, 0.17 mmol) was obtained 22 mg (33%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 8.45 (bs, 1H), 8.30 (d, J = 5.4 Hz, 1H), 7.50 (bs, 1H), 7.38 (d, J = 5.4 Hz, 1H), 7.05 (bs, 1H), 3.91 (s, 3H), 2.78(s, 3H), 2.69 (s, 6H).

EXAMPLE 64

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00190] From 6-bromo-4-chlorothieno[3,2-*d*]pyrimidine (21 mg, 0.08 mmol) and 5-methoxy-*N*1,*N*1-dimethylbenzene-1,3-diamine (17 mg, 0.08 mmol) was obtained 15 mg (41%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 8.85 (s, 1H), 7.75 (s, 1H), 7.55 (bs, 1H), 7.25 (bs, 1H), 7.08 (bs, 1H), 3.91 (s, 3H), 3.28 (s, 6H).

EXAMPLE 65

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00191] From 4-chloro-2-methylthieno[3,2-*d*]pyrimidine (150 mg, 0.82 mmol) and 3-methoxy-5-(1*H*-tetrazol-1-yl)benzenamine (144 mg, 0.82 mmol) was obtained 195 mg (63%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 9.83 (s, 1H), 8.89 (s, 1H), 8.02 (bs, 1H), 7.54 (bs, 1H), 7.50 (d, J = 5.4 Hz, 1H), 7.46 (bs, 1H), 3.96 (s, 3H), 2.80 (s, 3H).

EXAMPLE 66

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine

[00192] a) 2-Methylthieno[3,2-*d*]pyrimidin-4-ol. To an oven-dried sealed reaction flask charged with a magnetic stir bar at rt was added 3-amino-thiophene-2-carboxylic acid methyl ester (1.00 g, 6.36 mmol) and anhydrous acetonitrile (30 mL). To the resulting clear solution was bubbled $HCl_{(g)}$ until a white precipitate formed (~2 to 3 min). The white suspension was then transferred to an oil bath and heated at 110°C for 6 h. The solution was cooled to rt and the resulting white precipitate was removed by filtration through a buchner funnel. The filtrate was concentrated to a yellow solid by rotary evaporation. The solid was diluted in H_2O and filtered through a buchner funnel. The filtrate was basified (pH > 7) using $NaHCO_{3(aq)}$ whereupon a white precipitate formed. The precipitate was filtered, collected, and washed with H_2O and hexanes to give 0.665 g (62%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6) 8.13 (d, J = 5.2 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 2.37 (s, 3H).

[00193] b) 4-Chloro-2-methylthieno[3,2-*d*]pyrimidine. To an oven-dried one-neck reaction flask charged with a magnetic stir bar at rt under argon was added 2-methylthieno[3,2-*d*]pyrimidin-4-ol (0.500 g, 3.01 mmol), 1,2-dichloroethane (20 mL) and anhydrous dimethylformamide (0.58 mL, 7.5 mmol). The white suspension was cooled to 0°C, and to it was added distilled phosphorous oxychloride (0.70 mL, 7.5 mmol), then the suspension was refluxed for 2 h at 150°C. The resulting yellow solution was cooled to rt, quenched over ice (15 mL) and then 2N NaOH was added until the pH = 7. The neutralized solution was then extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to yield 0.54 g (99%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6) 8.55 (d, J = 5.5 Hz, 1H), 7.66 (d, J = 5.5 Hz, 1H), 2.74 (s, 3H).

[00194] c) 6-Bromo-4-chloro-2-methylthieno[3,2-*d*]pyrimidine. To an oven-dried three-neck reaction flask charged with a magnetic stir bar and an addition funnel at rt under argon was added anhydrous THF (35 mL) and lithium diisopropylamide mono(tetrahydrofuran) (1.5M solution in cyclohexane, 14.1 mL, 21.2 mmol). The yellow solution was cooled to -78°C (internal thermometer) over 15 min. A yellow suspension of 4-chloro-2-methylthieno[3,2-*d*]pyrimidine (2.62 g, 14.1 mmol) and THF (27.6 mL) was added dropwise from the addition funnel to the reaction solution. The yellow suspension was added over the course of 35 min while maintaining the internal temperature below -73°C. Once the addition was complete, the reaction suspension was cooled to -78°C and stirred for 15 minutes. To the reaction mixture was added via the addition funnel dropwise 1,2-dibromo-1,1,2,2-tetrafluoroethane (1.90 mL, 15.5 mmoL) while maintaining the internal temperature below -72°C. The reaction suspension was stirred at -78°C for approximately 15 min and then was equilibrated to rt and stirred overnight. The solvent was removed by rotary evaporation, diluted with water (100 mL), and extracted with $CHCl_3$ (3 x 200 mL). The extracts were dried over Na_2SO_4, filtered and then concentrated to yield a brown solid. It was purified by flash column chromatography (silica gel, gradient elution with EtOAc:Hexanes, 1:20) to give 0.430 g (11%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 7.51 (s, 1H), 2.81 (s, 3H).

[00195] d) 6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine. The title compound was prepared by a procedure similar to that of

Example 33. From 6-bromo-4-chloro-2-methylthieno[3,2-*d*]pyrimidine (0.044 g, 0.17 mmol) and 5-methoxy-*N1*,*N1*-dimethylbenzene-1,3-diamine (0.028 mL, 0.17 mmol) was obtained 0.005 g (8%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 7.43 (br s, 1H), 7.28 (s, 1H), 6.39-6.37 (m, 1H), 6.34-6.33 (m, 1H), 6.24-6.23 (m, 1H), 3.80 (s, 3H), 2.97 (s, 6H), 2.60 (s, 3H).

EXAMPLE 67

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00196] The title compound was prepared by a procedure similar to that of Example 33. From 6-bromo-4-chloro-thieno[3,2-*d*]pyrimidine (0.010 g, 0.040 mmol) and 3,5-dimethoxyaniline (0.006 mL, 0.040 mmol) was obtained 0.004 g (25%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) 8.63 (s, 1H), 7.41 (s, 1H), 6.87 (br s, 1H), 6.65 (d, J = 2.2 Hz, 2H), 6.40 (t, J = 2.2 Hz, 1H), 3.82 (s, 3H).

EXAMPLE 68

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00197] A mixture of *N*-(3-methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride (0.80 g, 2.2 mmol), concentrated hydrochloride (0.5 mL) and 5% palladium on carbon (400 mg) in ethanol (100 mL) and water (6 mL) was hydrogenated under 48 psi of hydrogen for 5 h. It was filtered and the solution was evaporated to give 0.21 g (27 %) of the title compound. ^{1}H NMR (DMSO-d_6) 11.13 (brs, 1H), 8.89 (s, 1H), 8.49 (d, J = 5.7 Hz, 1H), 7.58 (d, J = 5.4 Hz, 1H), 7.20 (brs, 2H), 6.65 (s, 1H), 3.78 (s, 3H).

EXAMPLE 69

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00198] To a mixture of *N*-(3-amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine (78 mg, 0.25 mmol) in methanol (10 mL) was added 37% aqueous formaldehyde (205 mg, 2.53 mmol) and 6 drops of acetic acid. It was stirred at rt for 1 h, then was cooled to 0°C. To the solution was added sodium cyanoborohydride (160 mg, 2.53 mmol) and it

was stirred at rt overnight. It was evaporated and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with water (30 mL), dried and evaporated and the residue was purified by column chromatography (dichlormethane/methanol 30 :1) to give 30 mg (40%) of the title compound. ^{1}H NMR ($CDCl_3$) 8.67 (s, 1H), 7.79 (d, J = 5.4 Hz, 1H), 7.40 (d, J = 5.4 Hz, 1H), 6.48 (m, 2H), 6.21 (t, J = 2.4 Hz, 1H), 3.81 (s, 3H), 2.97 (s, 6H).

EXAMPLE 70

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride

[00199] a) 3-Methoxy-*N*,*N*-dimethyl-5-nitrobenzenamine. To a solution of 3-methoxy-5-nitrobenzenamine (1.40 g, 8.33 mmol) in methanol (10 mL) was added acetic acid (0.5 mL) and aqueous formaldehyde (2.5 g). The solution was stirred at rt for 1 h and cooled to 0°C. To the mixture was added sodium cyanoborohydride (5.23 g, 83.3 mmol) portionwise and it was stirred at rt overnight. It was evaporated under vacuum, and the residue was mixed with ethyl acetate (30 mL) and washed with water. The organic layer was dried, concentrated and the residue was purified by column chromatography (Hexane/EtOAc 3:1) to give 0.52 g (32%) of the title compound. ^{1}H NMR ($CDCl_3$) 7.19(t, J = 2.1 Hz, 1H), 7.09 (t, J = 2.1 Hz, 1H), 6.46 (t, J = 2.1 Hz, 1H), 3.86 (s, 3H), 3.02 (s, 6H).

[00200] b) 5-Methoxy-*N*1,*N*1-dimethylbenzene-1,3-diamine hydrochloride. A solution of 3-methoxy-*N*,*N*-dimethyl-5-nitrobenzenamine (0.53 g, 2.7 mmol) and 5% palladium on carbon (130 mg) in ethanol (50 mL) with 5 drops of concentrated hydrochloride was hydrogenated under 48 psi for 6 h. It was filtered and the filtrate was evaporated to give 0.45 g (83 %) of the title compound as hydrochloride salt.

[00201] c) *N*-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride. The title compound was prepared by a procedure similar to Example 33. From 4-chlorothieno[3,2-*d*]pyrimidine (376 mg, 1.86 mmol) and 5-methoxy-*N*1,*N*1-dimethylbenzene-1,3-diamine (316 mg, 1.86 mmol) in isopropanol was obtained 500 mg (80%) of the title compound as a solid. ^{1}H NMR (CD_3OD) 8.92 (s, 1H), 8.53 (d, J = 5.7 Hz, 1H), 7.70 (brs, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.40 (brs, 1H), 7.15 (brs, 1H), 3.92 (s, 3H), 3.30 (s, 6H).

EXAMPLE 71

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00202] To a solution of *N*-(3-amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine in acetic acid (3.0 mL) and concentrated sulfuric acid (0.3 mL) kept at 0°C was added sodium nitrite (15 mg, 0.22 mmol) in water (1.0 mL). It was stirred at 0°C for 20 min, and a solution of sodium azide (14 mg, 0.22 mmol) in water (1.0 mL) was added. The solution was stirred at 0°C for 2 h, and poured into ice water. It was extracted with ethyl acetate, and the extracts were dried and evaporated. The residue was purified by column chromatography (Hexane/EtOAc 1:1) to give 11 mg (25%) of the title compound. ^{1}H NMR ($CDCl_3$) 8.76 (s, 1H), 7.79 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.06 (t, J = 2.1 Hz, 1H), 6.99 (t, J = 2.1 Hz, 1H), 6.43 (t, J = 2.1 Hz, 1H), 3.84 (s, 3H).

EXAMPLE 72

N-(5-Amino-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00203] To a hydrogenation reaction flask was added *N*-(2-methoxy-5-nitrophenyl)-thieno[3,2-*d*]pyrimidin-4-amine (0.015 g, 0.050 mmol), EtOH (2 mL), EtOAc (2 mL), and Pd/C (5%, 0.005 g) and then the black suspension was degassed three times and filled with $H_{2(g)}$ (35 psi). The black suspension was shaken at rt for 2 h, filtered through celite, washed with additional EtOAc (70 mL), dried over $MgSO_4$ and concentrated to give a yellow solid. It was purified by flash column chromatography (silica gel, with EtOAc) to give 0.002 g (15%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$) 8.77 (s, 1H), 8.06 (d, J = 2.7 Hz, 1H), 7.77 (dd, J = 5.2 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H), 7.34 (br s, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.44 (dd, J = 8.5 and 2.7 Hz, 1H), 3.88 (s, 3H), 3.63 (br s, 2H).

EXAMPLE 73

N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine

[00204] A suspension of *N*-(3-amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride (65 mg, 0.210 mmol) in a mixture of water (2 mL) and methanol (1 mL) was cooled to 0°C. To the suspension was added drop wise a solution of bromine (120

mg, 0.751 mmol) in water (1 mL) and glacial acetic acid (1 mL). The reaction mixture was stirred at 0°C for 10 min, diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (75% ethyl acetate/hexane) to give the title compound (102 mg, 95%). ^1H NMR ($CDCl_3$) 8.66 (s, 1H), 7.68 (d, 1H, $J = 5.4$ Hz), 7.41 (d, 1H, $J = 5.7$ Hz), 4.92 (s, 2H), 3.90 (s, 3H).

EXAMPLE 74

N-(3-Dimethylamino-5-methoxyphenyl)-thieno[2,3-*d*]pyrimidin-4-amine

[00205] The title compound was prepared in a manner similar to example 33. From 4-chloro-thieno[2,3-*d*]pyrimidine (0.015 g, 0.090 mmol) and 5-methoxy-*N1*,*N1*-dimethyl-benzene-1,3-diamine (0.015 g, 0.090 mmol) was obtained 0.007 g (26%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) 8.61 (s, 1H), 7.31 (d, $J = 6.0$ Hz, 1H), 7.07 (d, $J = 6.0$ Hz, 1H), 6.94 (br s, 1H), 6.63 (t, $J = 1.9$ Hz, 1H), 6.57 (t, $J = 2.0$ Hz, 1H), 6.13 (t, $J = 2.2$ Hz, 1H), 3.82 (s, 3H), 2.97 (s, 6H).

EXAMPLE 75

Identification of *N*-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine and Analogs as Caspase Cascade Activators and Inducers of Apoptosis in Solid Tumor Cells

[00206] Human breast cancer cell line T-47D, human lung cancer cell line H1299, human hepatocellular carcinoma cell line SNU398, human colon carcinoma cell line HCT116 were grown according to media component mixtures designated by American Type Culture Collection + 10% FCS (Invitrogen Corporation), in a 5 % CO_2 –95 % humidity incubator at 37 °C. T-47D and H1299 cells were maintained at a cell density between 50 and 80 % confluency at a cell density of 0.1 to 0.6 x 10^6 cells/mL. Cells were harvested at 600xg and resuspended at 0.65 x 10^6 cells/mL into appropriate media + 10 % FCS. An aliquot of 22.5 µL of cells was added to a well of a 384-well microtiter plate containing 2.5 µL of a 10 % DMSO in RPMI-1640 media solution containing 0.16 to 100 µM of *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine or other test compound (0.016 to 10 µM final). An aliquot of 22.5 µL of cells was added to a well of a 384-well

microtiter plate containing 2.5 μL of a 10 % DMSO in RPMI-1640 media solution without test compound as the control sample. The samples were mixed by agitation and then incubated at 37 °C for 24 h or 48 h in a 5 % CO_2-95 % humidity incubator. After incubation, the samples were removed from the incubator and 25 μL of a solution containing 14 μM of *N*-(Ac-DEVD)-*N'*-ethoxycarbonyl-R110 (SEQ ID No.:1) fluorogenic substrate (Cytovia, Inc.; WO99/18856), 20 % sucrose (Sigma), 20 mM DTT (Sigma), 200 mM NaCl (Sigma), 40 mM Na PIPES buffer pH 7.2 (Sigma), and 500 μg/mL lysolecithin (Calbiochem) was added. The samples were mixed by agitation and incubated at room temperature. Using a fluorescent plate reader (Model SPECTRAfluor Plus, Tecan), an initial reading (T = 0) was made approximately 1-2 min after addition of the substrate solution, employing excitation at 485 nm and emission at 530 nm, to determine the background fluorescence of the control sample. After the 3 h incubation, the samples were read for fluorescence as above (T = 3 h).

Calculation:

[00207] The Relative Fluorescence Unit values (RFU) were used to calculate the sample readings as follows:

$$RFU_{(T=3h)} - \text{Control } RFU_{(T=0)} = \text{Net } RFU_{(T=3h)}$$

[00208] The activity of caspase cascade activation was determined by the ratio of the net RFU value for *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine or other test compound to that of control samples. The EC_{50} (nM) was determined by a sigmoidal dose-response calculation (Prism 3.0, GraphPad Software Inc.).

[00209] The caspase activation potency (EC_{50}) are summarized in Table I:

Table I. Caspase activation Potency

Example	EC_{50} (nM)				
	T47D (24 h)	T-47D (48 h)	H1299 (24 h)	SNU398 (48 h)	HCT116 (48 h)
1	65	40	1548	557	2329
2	61	105	2911	1613	5003
3	121	311	4999	4662	5554
4	>10000	>10000	>10000	>10000	>10000

Example	EC_{50} (nM)				
	T47D (24 h)	T-47D (48 h)	H1299 (24 h)	SNU398 (48 h)	HCT116 (48 h)
5	147	296	>10000	>10000	>10000
6	>10000	>10000	>10000	>10000	>10000
7	>10000	>10000	>10000	>10000	>10000
8	>10000	>10000	>10000	>10000	>10000
9	>10000	>10000	>10000	>10000	>10000
10	65	72	5024	1053	4995
11	555	1186	5374	5734	>10000
12	38	62	303	249	279
13	>10000	>10000	>10000	>10000	>10000
14	1811	2021	>10000	>10000	>10000
15	5741	5464	5078	5277	>10000
16	>10000	>10000	>10000	>10000	>10000
17	36	105	299	534	346
18	71	171	2792	>10000	>10000
19	>10000	>10000	>10000	>10000	>10000
20	16	37	114	431	341
21	>10000	>10000	>10000	>10000	>10000
22	114	233	5025	>10000	341
23	>10000	>10000	>10000	>10000	>10000
24	>10000	>10000	>10000	>10000	>10000
25	5566	>10000	5436	>10000	>10000
26	476	496	5042	>10000	>10000
27	20	36	41	206	319
28	422	542	>10000	>10000	>10000
29	>10000	>10000	>10000	>10000	>10000
30	>10000	>10000	5109	>10000	>10000
31	417	519	>10000	>10000	>10000
32	2074	4015	1417	1596	4247
33	>10000	>10000	>10000	>10000	>10000

Example	EC_{50} (nM)				
	T47D (24 h)	T-47D (48 h)	H1299 (24 h)	SNU398 (48 h)	HCT116 (48 h)
34	>10000	>10000	>10000	>10000	>10000
35	>10000	>10000	>10000	>10000	>10000
36	>10000	873	5091	5180	>10000
37	5072	5332	5059	3568	>10000
38	>10000	>10000	>10000	>10000	>10000
39	>10000	6903	>10000	>10000	>10000
40	5244	2139	5486	4851	>10000
41	>10000	>10000	>10000	>10000	>10000
42	>10000	>10000	>10000	>10000	>10000
43	>10000	>10000	>10000	>10000	>10000
44	1102	ND	2684	ND	ND
45	ND	87	ND	>10000	>10000
46	ND	1517	ND	>10000	>10000
47	ND	>10000	ND	>10000	>10000
48	ND	1991	ND	>10000	>10000
49	ND	>10000	ND	>10000	>10000
50	ND	4358	ND	10000	10000
51	ND	2493	ND	2639	3704
52	32	33	ND	468	82
53	ND	723	ND	868	2448
54	27	30	ND	256	61
55	112	99	ND	>10000	>10000
56	ND	1839	ND	1034	2609
57	ND	>10000	ND	>10000	>10000
58	>10000	565	ND	168	347
59	ND	>10000	ND	3255	>10000
60	ND	>10000	ND	>10000	>10000
61	355	287	ND	138	291
62	>10000	>10000	>10000	>10000	>10000

Example	EC_{50} (nM)				
	T47D (24 h)	T-47D (48 h)	H1299 (24 h)	SNU398 (48 h)	HCT116 (48 h)
63	ND	320	ND	706	1257
64	ND	131	ND	565	1279
65	ND	457	ND	354	620
66	ND	65	ND	297	498
67	ND	227	ND	4948	>10000
68	ND	2949	ND	5083	>10000
69	ND	191	ND	251	323
70	ND	241	ND	238	433
71	ND	209	ND	262	144
72	>10000	>10000	>10000	>10000	>10000
73	ND	486	ND	605	1668

ND, not determined.

[00210] Thus, *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine (Example 1) and analogs are identified as potent caspase cascade activators and inducers of apoptosis in solid tumor cells.

[00211] Several compounds were also tested in other cancer cells lines (48 h assay), including human lymphoma cell line Raji, human B cell lymphoblastoid cell line Ramos, human Burkitt's lymphoma cell line Namalwa, and breast cancer cell line SKBR3, and the data are summarized in Table II.

Table II. Caspase Activation Potency

Example	EC_{50} (nM) (48 h)			
	Raji	Ramos	Namalwa	SKBR3
12	ND	582	356	77
70	399	173	204	153

ND, not determined.

[00212] Thus, these data indicated that *N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine (Example 12) and analogs are potent caspase cascade activators and inducers of apoptosis in several tumor cells.

EXAMPLE 76

Identification of *N*-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine and Analogs as Antineoplastic Compound That Inhibits Cell Proliferation (GI_{50})

[00213] Human breast cancer cell lines T-47D, MX-1 and MDAMB435, human colon cancer cell line HT29, and human lung cancer cell line H1299 were grown and harvested as in Example 75. An aliquot of 90 μL of cells (4.4×10^4 cells/mL) was added to a well of a 96-well microtiter plate containing 5 μL of a 10 % DMSO in RPMI-1640 media solution containing 10 nM to 100 μM of *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine (1 nM to 10 μM final). An aliquot of 45 μL of cells was added to a well of a 96-well microtiter plate containing 5 μL of a 10 % DMSO in RPMI-1640 media solution without compound as the control sample for maximal cell proliferation (L_{Max}). The samples were mixed by agitation and then incubated at 37 °C for 48 h in a 5% CO_2-95% humidity incubator. After incubation, the samples were removed from the incubator and 25 μL of CellTiter-Glo ™ reagent (Promega) was added. The samples were mixed by agitation and incubated at room temperature for 10-15 min. Plates were then read using a luminescent plate reader (Model SPECTRAfluor Plus, Tecan) to give L_{test} values.

[00214] Baseline for GI_{50} (dose for 50% inhibition of cell proliferation) of initial cell numbers was determined by adding an aliquot of 45 μL of cells or 45 μL of media, respectively, to wells of a 96-well microtiter plate containing 5 μL of a 10% DMSO in RPMI-1640 media solution. The samples were mixed by agitation and then incubated at 37 °C for 0.5 h in a 5% CO_2-95% humidity incubator. After incubation, the samples were removed from the incubator and 25 μL of CellTiter-Glo ™ reagent (Promega) was added. The samples were mixed by agitation and incubated at 37 °C for 10-15 min at room temperature in a 5% CO_2-95% humidity incubator. Fluorescence was read as above, (L_{Start}) defining luminescence for initial cell number used as baseline in GI_{50} determinations.

Calculation:

[00215] GI_{50} (dose for 50% inhibition of cell proliferation) is the concentration where $[(L_{Test} - L_{Start}) / (L_{Max} - L_{Start})] = 0.5$.

[00216] The GI_{50} (nM) are summarized in Table III:

Table III. GI_{50} in Cancer Cells

Example	GI_{50} (nM)				
	T47D	**MX1**	**MDAMB435**	**H1299**	**HT29**
1	80	300	295	1170	3554
2	65	300	756	1043	3632
5	200	300	>10000	>10000	>10000
6	>10000	>10000	>10000	>10000	>10000

[00217] Thus, *N*-(2,5-dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine (Example 1) and analogs are identified as antineoplastic compound that inhibits cell proliferation.

[00218] Several compounds were tested in multi cancer cell lines, including human breast cancer cell lines T-47D, MX-1, SKBR3 and MDAMB435, human hepatocellular carcinoma cell line SNU398, human colon carcinoma cell line HCT116, human sarcoma cell line MES-SA and multi-drug resistant (MDR) human sarcoma cell line MES-SA/ADR, murine leukemia cell line P388 and multi-drug resistant (MDR) murine leukemia cell line P388ADR, and the data are summarized in Table IV.

Table IV. GI_{50} in Multi-Cancer Cells

	GI_{50} (nM)					
Example	**2**	**12**	**54**	**61**	**69**	**71**
T47D	340	20	40	398	133	208
SNU398	2104	706	1073	299	276	305

	GI_{50} (nM)					
Example	**2**	**12**	**54**	**61**	**69**	**71**
HCT116	4981	1253	6579	400	300	300
MX1	800	17	100	791	9853	1673
MDAMB 435	1070	105	121	61	41	92
SKBR3	500	60	ND	600	100	200
MES-SA	5190	364	788	836	600	385
MES-SA/ ADR	7256	1198	2000	767	520	796
P388	2065	540	1047	280	381	218
P388/ADR	2599	296	1104	199	249	157

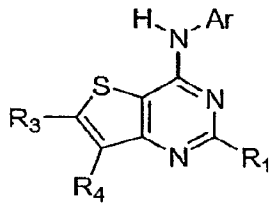
ND, not determined.

[00219] Thus, *N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine (Example 2) and analogs are identified as antineoplastic compound that inhibits cell proliferation in several cancer cell lines. More importantly, these compounds were found to have similar activity against MES-SA and its corresponding multi-drug resistant cell MES-SA/ADR, as well as P388 and its corresponding multi-drug resistant cell P388/ADR.

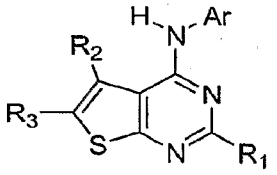
[00220] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A method of treating a disorder responsive to the induction of apoptosis in an animal suffering therefrom, comprising administering to an animal in need of such treatment an effective amount of a compound having the Formulae I and II:



(I)



(II)

or pharmaceutically acceptable salts or prodrugs or tautomers thereof, wherein:

Ar is optionally substituted aryl or optionally substituted heteroaryl;

R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol; and

R_2-R_4 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

2. The method of claim 1, wherein said animal is a mammal.

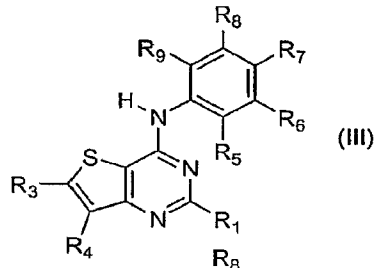
3. The method of claim 1, wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

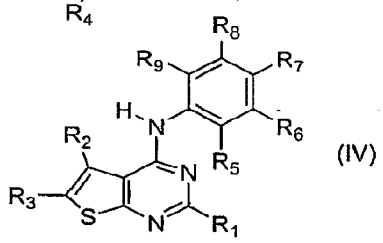
4. The method of claim 1, wherein R_2 is hydrogen.

5. The method of claim 1, wherein R_3 is hydrogen or halogen.

6. The method of claim 1, wherein Ar is optionally substituted and is phenyl or pyridyl.

7. A method of treating a disorder responsive to the induction of apoptosis in an animal suffering therefrom, comprising administering to an animal in need of such treatment an effective amount of a compound having the Formulae III-IV:


(III)


(IV)

or a pharmaceutically acceptable salt or prodrug or tautomer thereof, wherein:

R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol;

R_2-R_9 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol.

8. The method of claim 7, wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

9. The method of claim 7, wherein R_2 is hydrogen.

10. The method of claim 7, wherein R_3 is hydrogen or halogen.

11. The method of claim 8, wherein R_6 or R_8 is alkoxy or amino.

12. The method of claim 8, wherein both R_6 and R_8 are alkoxy.

13. A method of treating a disorder responsive to the induction of apoptosis in an animal suffering therefrom, comprising administering to an animal in need of such treatment an effective amount of a compound selected from the group consisting of:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;
N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;
6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(2-methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-5-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate;

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride;
N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3-Dimethylamino-5-methoxyphenyl)-thieno[2,3-*d*]pyrimidin-4-amine;
or a pharmaceutically acceptable salt or prodrug thereof.

14. The method of claim 1, 7 or 13, wherein said disorder is cancer.

15. The method according to claim 14, wherein said cancer is Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, chronic lymphocytic leukemia, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, malignant melanoma, choriocarcinoma, mycosis fungoide, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, or prostatic carcinoma.

16. The method of claim 14, wherein said cancer is drug resistant cancer.

17. The method of claim 14, further comprising administering at least one known cancer chemotherapeutic agent, or a pharmaceutically acceptable salt of said agent.

18. The method according to claim 14, wherein said compound is administered together with at least one compound selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-

fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan, chlorambucil, cyclophosamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, Herceptin®, Rituxan®, arsenic trioxide, gemcitabine, doxazosin, terazosin, tamsulosin, CB-64D, CB-184, haloperidol, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, BMS-232,632, bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, fenretinide, N-4-carboxyphenyl retinamide, lactacystin, MG-132, PS-341, Gleevec®, ZD1839 (Iressa), SH268, genistein, CEP2563, SU6668, SU11248, EMD121974, R115777, SCH66336, L-778,123, BAL9611, TAN-1813, flavopiridol, UCN-01, roscovitine, olomoucine, celecoxib, valecoxib, rofecoxib and alanosine.

19. The method of claim 14, further comprising treating said animal with radiation-therapy.

20. The method of claim 14, wherein said compound is administered after surgical treatment of said animal for said cancer.

21. The method of claim 1, 7 or 13, wherein said disorder is an autoimmune disease.

22. The method of claim 1, 7 or 13, wherein said disorder is an infectious viral disease.

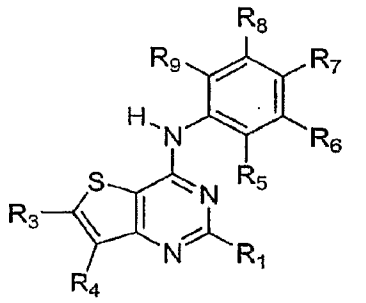
23. The method of claim 1, 7 or 13, wherein said disorder is rheumatoid arthritis.

24. The method of claim 1, 7 or 13, wherein said disorder is an inflammatory disease.

25. The method of claim 1, 7 or 13, wherein said disorder is a skin disease.

26. The method of claim 1, 7 or 13, wherein said disorder is psoriasis.

27. A compound having the Formula III:



(III)

or a pharmaceutically acceptable salt or prodrug or tautomer thereof, wherein:

R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl; arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol;

R_3-R_9 independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, sulfone, sulfoxide, acyloxy, azido, carboxy, methylenedioxy, carbonylamido or alkylthiol; and

with the proviso that when one or both of the R_6 or R_8 is methoxy, then R_3 is not phenyl or 4-*t*-bu-phenyl, or R_7 is not 2-methoxybenzylozy.

28. The compound of claim 27, wherein R_1 is hydrogen, halo, optionally substituted amino, optionally substituted alkylthiol, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted C_{1-10} alkyl.

29. The compound of claim 27, wherein R_3 is hydrogen or halogen.

30. The compound of claim 27, wherein one of the R_6 or R_8 is alkoxy or amino.

31. The compound of claim 27, wherein both R_6 and R_8 are alkoxy.

32. The compound of claim 27, wherein said compound is selected from the group consisting of:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,4-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;
6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2-methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine;
3-[4-(Thieno[3,2-*d*]pyrimidin-4-ylamino)-phenyl]acrylic acid ethyl ester;
N-(5-Methoxy-2-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(2-Methoxy-5-phenoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
4-Methoxy-3-(thieno[3,2-*d*]pyrimidin-4-ylamino)-benzoic acid;
N-(2-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,5-Dihydroxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate;

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Bis(methylsulfonyl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,6-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride;

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Amino-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

or a pharmaceutically acceptable salt or prodrug thereof.

33. The compound of claim 27, wherein said compound is selected from the group consisting of:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,4,5-Trimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

6-Iodo-*N*-(2,5-dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(2,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-methoxy-5-methylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Dimethoxyphenyl)-6-phenylthieno[3,2-*d*]pyrimidin-4-amine;

N-(2,5-Diethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(2-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Chloro-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(5-*tert*-Butyl-2-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Hydroxy-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-7-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-bromo-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-6-iodothieno[3,2-*d*]pyrimidin-4-amine;

N-(3,5-Dimethoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

N-(5-Methoxy-3-trifluoromethylphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

Dimethyl 5-(thieno[3,2-*d*]pyrimidin-4-ylamino)benzene-1,3-dioate;

N-(3-Methoxy-5-nitrophenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Methoxy-5-(1*H*-tetrazol-1-yl)phenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3-dimethylamino-5-methoxyphenyl)-2-methylthieno[3,2-*d*]pyrimidin-4-amine;

6-Bromo-*N*-(3,5-dimethoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Dimethylamino-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine hydrochloride;

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

N-(3-Amino-2,4,6-tribromo-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;

or a pharmaceutically acceptable salt or prodrug thereof.

34. The compound of claim 27, wherein both R_5 and R_8 are not hydrogen.

N-(3-Azido-5-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4-amine;
or a pharmaceutically acceptable salt or prodrug thereof.

38. A compound selected from the group consisting of:

N-(2,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)thieno[2,3-*d*]pyrimidin-4-amine;
N-(3,5-Dimethoxyphenyl)-2-methylthieno[2,3-*d*]pyrimidin-4-amine;
N-(3-Dimethylamino-5-methoxyphenyl)-thieno[2,3-*d*]pyrimidin-4-amine;
or a pharmaceutically acceptable salt or prodrug thereof.

39. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of any one of claims 27-38.

40. The pharmaceutical composition of claim 39, further comprising at least one known cancer chemotherapeutic agent, or a pharmaceutically acceptable salt of said agent.

41. The pharmaceutical composition of claim 39, further comprising at least one compound selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan, chlorambucil, cyclophosamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, Herceptin®, Rituxan®, arsenic trioxide, gemcitabine, doxazosin, terazosin, tamsulosin, CB-64D, CB-184, haloperidol, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, BMS-232,632, bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, fenretinide, N-4-carboxyphenyl retinamide, lactacystin, MG-132, PS-341, Gleevec®, ZD1839 (Iressa), SH268, genistein, CEP2563, SU6668, SU11248, EMD121974, R115777, SCH66336, L-778,123,

BAL9611, TAN-1813, flavopiridol, UCN-01, roscovitine, olomoucine, celecoxib, valecoxib, rofecoxib and alanosine.